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Articolul 1. Performance of Ultrasound Techniques and the Potential of Artificial Intelligence in the Evaluation of Hepatocellular Carcinoma and Non-Alcoholic Fatty Liver Disease.
Lupsor-Platon, M.; Serban, T.; Silion, A.I.; Tirpe, G.R.; Tirpe, A**.; Florea, M.** *Cancers*, **2021,** *13*, 790. https://doi.org/10.3390/cancers13040790. **IF= 6,126; Q1.**
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Articolul 2. Hepatocellular Carcinoma and Non-Alcoholic Fatty Liver Disease: A Step Forward for Better Evaluation Using Ultrasound Elastography. Lupsor-Platon, M.; Serban, T.; Silion, A.-I.; Tirpe, A.; **Florea, M.** *Cancers* **2020**, *12*; 2778. https://doi.org/10.3390/cancers12102778. **IF= 6,126; Q1. Link WOS:** https://www.webofscience.com/wos/woscc/full-record/WOS:000584177500001; **pagina 25 (25-53).**

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Review

Performance of Ultrasound Techniques and the Potential of Artificial Intelligence in the Evaluation of Hepatocellular Carcinoma and Non-Alcoholic Fatty Liver Disease

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Simple Summary: The increasing prevalence of non-alcoholic fatty liver disease (NAFLD) represents a challenge for the current medical systems. If NAFLD is left undetected and untreated, it can progress towards fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). To date, ultrasonography (US) is the first-line examination indicated to NAFLD patients that also screens for other focal liver lesions (FLLs). The downside of conventional B-mode US is that it cannot accurately quantify steatosis and fibrosis and cannot further characterize FLL certainly—is it cancer or is it not? Ultrasound contrast agents (UCAs) allowed physicians to further evaluate the FLL for the diagnosis of HCC. This review discusses the performance of US techniques in NAFLD and NAFLD-related HCC diagnosis, as well as of artificial intelligence (AI)-based methods, specifically the usefulness and assistance of deep learning algorithms for improving liver US image processing.

Abstract: Global statistics show an increasing percentage of patients that develop non-alcoholic fatty liver disease (NAFLD) and NAFLD-related hepatocellular carcinoma (HCC), even in the absence of cirrhosis. In the present review, we analyzed the diagnostic performance of ultrasonography (US) in the non-invasive evaluation of NAFLD and NAFLD-related HCC, as well as possibilities of optimizing US diagnosis with the help of artificial intelligence (AI) assistance. To date, US is the first-line examination recommended in the screening of patients with clinical suspicion of NAFLD, as it is readily available and leads to a better disease-specific surveillance. However, the conventional US presents limitations that significantly hamper its applicability in quantifying NAFLD and accurately characterizing a given focal liver lesion (FLL). Ultrasound contrast agents (UCAs) are an essential add-on to the conventional B-mode US and to the Doppler US that further empower this method, allowing the evaluation of the enhancement properties and the vascular architecture of FLLs, in comparison to the background parenchyma. The current paper also explores the new universe of AI and the various implications of deep learning algorithms in the evaluation of NAFLD and NAFLD-related HCC through US methods, concluding that it could potentially be a game changer for patient care.

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1. Introduction

Hepatocellular carcinoma (HCC), the fourth leading cause of cancer mortality worldwide and the fifth and ninth most commonly diagnosed cancer in men and women, respectively, has changed its landscape. The incidence of non-viral HCC is increasing, since obesity, metabolic syndrome (MetS), and type 2 diabetes mellitus are a true epidemic [1,2]. Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the MetS, has become one of the leading causes of morbidity and mortality globally, affecting approximately 25% of the world's population [3,4]. NAFLD diagnosis requires identifying steatosis by imaging methods or histology, as well as the exclusion of significant alcohol consumption or other competing etiologies for fat accumulation [5–8]. The burden of NAFLD is especially important since it can progress towards fibrosis, cirrhosis, and NAFLD-related HCC [4]. Moreover, this pathology is recognized not only as the most common etiology of chronic liver disease, but as a major cause of cirrhosis and HCC, and it is expected to become the leading recommendation for liver transplantation in this decade [9,10]. Mittal et al. [11] reported that NAFLD individuals are fivefold more likely to develop HCC without underlying cirrhosis, compared to patients suffering from other chronic liver diseases. Notably, most NAFLD patients included in this study suffered from obesity and diabetes, supporting the pathogenetic hypothesis. The carcinogenesis process behind the HCC development in NAFLD is not completely understood, but different metabolic comorbidities, such as obesity and insulin resistance, are being incriminated, along with the pro-inflammatory status and the genetic predisposition identified in some patients [12]. It is well known that the presence and severity of fibrosis are important prognostic factors in NAFLD. Using combinations of non-invasive methods, such as composite scoring systems and/or transient elastography, enabled risk stratification of patients by fibrosis stage [13,14].

At present, ultrasonography (US) is the first-line imaging modality used for HCC screening among cirrhotic patients. Having a sensitivity of 40–81% and specificity of 80–100% for surveillance purposes, US is useful in cirrhotic and noncirrhotic patients, including NAFLD that should also undergo routine surveillance [15,16]. However, this technology encounters several limitations in the NAFLD population, considering that the body mass index (BMI) among these subjects is usually increased [17]. In addition, current guidelines lack specific recommendations for primary HCC prevention and, moreover, do not include clear recommendations for a cost-effective surveillance of the non-cirrhotic NAFLD patients carrying a risk of HCC development [14,18]. Surveillance among these individuals remains controversial since mass screening using conventional US has low cost-effectiveness [19]. Evidence of improved non-invasive diagnosis is in growing progress, requiring updating and reflection of data in clinical practice. In this review, we provide an updated analysis of the performance of ultrasound techniques and the potential contribution of artificial intelligence-based methods in the US evaluation of NAFLD/NASH and NAFLD-related HCC.

2. Conventional Ultrasonography

2.1. Evaluating NAFLD Using Conventional US

Currently, conventional US is recommended as the first-line examination for patients with high clinical suspicion of NAFLD, given the large number of advantages: It is cost effective, broadly available, non-invasive, appropriate for re-examination, and highly convenient for patients [5–7,20,21]. Ultrasound is sensitive (85%) and specific (95%) for detecting moderate to severe steatosis (>33% steatotic hepatocytes), but its sensitivity deteriorates when <30% of hepatocytes are affected [21,22]. Moreover, increased echogenicity, the main US finding in NAFLD patients, is present in fibrosis and early cirrhosis as well, reducing the reliability of US in coexisting liver disease etiologies [13].

2.1.1. Ultrasound Diagnostic Criteria for Hepatic Steatosis

Besides hepatomegaly, the fat droplets interact with the ultrasound and a greater number of echoes return to transducer, displaying the well-known bright, hyperechoic liver, compared to the right kidney. Furthermore, the hyperechoic appearance of the liver results in a poor visualization of portal veins, liver capsule, and the gallbladder wall. In addition, lipids attenuate the ultrasound, leading to posterior darkness effect and a decreased visualization of the structures within the parenchyma and of the diaphragm, as seen in Figure 1. Also, altered liver hemodynamics detected with Doppler US can be seen, with one noteworthy example being the abnormal waveforms of the hepatic veins [20,21,23–25].

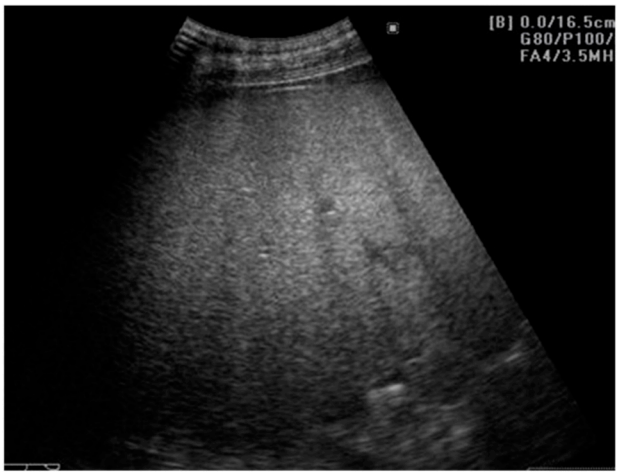


Figure 1. Hepatic steatosis. The 2D-US examination is showing an enlarged liver, with increased echogenicity and posterior beam attenuation, with a slightly inhomogeneous structure of fine granularity, without any FLLs. Even if this aspect is highly suggestive of hepatic steatosis, conventional US is unable to properly quantify the fatty amount of the liver. Also, 2D-US cannot specify whether fibrosis is present or not. Usually, steatosis and fibrosis coexist and therefore "steato-fibrosis" is the preferred term in this situation.

2.1.2. Quantitative Assessment of Hepatic Steatosis

The hyperechoic image is a qualitative feature and is dependent on the subjective interpretation of the examiner, leading to variability in results and low reproducibility [26]. A grading system of steatosis has been proposed in attempt to reduce the observer bias, using the hepatic, periportal, and diaphragmatic echogenicity, as exemplified in Table 1. However, all the criteria used to grade steatosis remain subjective.

Table 1. Criteria used in the B-mode US grading of steatosis [5,27].

Grade	Ultrasonographic Features
I: mild steatosis	Liver echogenicity slightly increased and normal visualization of portal vein wall and the diaphragmatic outline.
II: moderate steatosis	Liver echogenicity moderately increased with slightly impaired visualization of portal vein wall and diaphragmatic outline.
III: severe steatosis	Liver echogenicity markedly increased with poor or no visualization of portal vein wall, diaphragmatic outline, and posterior portion of the right hepatic lobe.

2.1.3. US Performance for Steatosis Detection

Conventional US is an accurate and highly reliable diagnostic tool for steatosis assessment. Wang et al. [28] found that the agreement rate of US as compared to histology is 61.4% in assessing the steatosis severity and 74.3% in diagnosing steatosis. A meta-analysis

by Hernaez et al. [22] estimated that the US sensitivity to detect moderate and severe steatosis confirmed by histology is 84.8% and the specificity is 93.6%. However, when mild steatosis is taken into consideration (fat content less than 20%), the traditional US has low sensitivity and therefore a high false negative rate of 55% [29]. The Dasarathy [29] prospective study observed that a combination of abnormal sonographic features increases the overall sensitivity and specificity. Another noteworthy remark was the fact that the sensitivity and specificity of hepatic vein blurring was higher than the one of the portal vein blurring, and there was a high concordance between hepatic vein blurring and the increased echogenicity. Therefore, the combination of portal vein blurring and liver brightness was a better sonographic predictor for hepatic steatosis [30].

Recently, a series of quantitative and semi-quantitative parameters have been implemented on US methods in order to overcome the limitation of low sensitivity in mild steatosis diagnosis. Some of these parameters exhibit a better performance than conventional US alone and have a better reproducibility and reliability [26,31–33]. Such parameters include attenuation (AC) and backscatter coefficients (BSC), the hepato-renal index (HRI) and ultrasound envelope statistic parametric imaging (known as speckle statistics). Hepatic steatosis correlates positively with these parameters. However, further studies are warranted to validate their potential widespread clinical use [31,34].

In addition, the controlled attenuation parameter (CAP) measured by the vibration controlled transient elastography (VCTE), a widely available device, has a powerful contribution in steatosis evaluation. The potential of US elastography is a subject of high interest in the non-invasive evaluation of NAFLD and NAFLD-related HCC, as previously exemplified in a recent paper from our group [14].

2.1.4. Ultrasonographic Steatosis Patterns

In the fatty liver, there are a number of different steatosis patterns that might be observed: diffuse, multinodular, focal geographic, focal nodular, intralesional, perilesional, subcapsular, periportal, perivenular steatosis, and hypersteatosis. Frequently, focal fatty infiltration occurs geographically, but pseudo-tumoral aspects are also possible [35]. Another mass like appearance can be given by areas of normal echogenicity as compared with the background hyperechoic parenchyma, termed "focal fatty sparing" (FFS). FFS are commonly found in segments IV and V, near the left portal vein or adjacent to the falciform ligament and the gallbladder fossa [36]. Due to their nodular appearance, FFS can lead to confusion with other focal liver lesions (FLLs) that have pathological implications.

2.1.5. Limitations of Ultrasonography in Steatosis Diagnosis

As previously mentioned, fibrosis is a key histologic feature that needs to be considered in NAFLD patients and especially in NASH subjects. Fibrosis is an important confounder for steatosis evaluation using US, as they both appear hyperechoic [37]. A study of 118 biopsy-proven NAFLD subjects found that US sensitivity for detecting moderate to severe histological steatosis was 100% among individuals with mild fibrosis on histology [37]. However, it decreased significantly to 77.8% in those with advanced fibrosis. In fact, several studies found no correlation between the US characteristics and the grade of inflammation, ballooning, and fibrosis identified on histology, making it challenging to distinguish between simple steatosis and progressive NASH [38,39]. Several studies proved that US was unable to discriminate between simple steatosis and NASH [29,40].

Another limitation of US is the low sensitivity in patients with morbid obesity (BMI > 40 kg/m^2) [41]. The subcutaneous fat reduces the ability of conventional US to evaluate liver echogenicity, especially among patients with high risk for NAFLD development [42]. In addition, as above mentioned, the method is unable to establish with certainty the degree of fatty infiltration.

2.2. NAFLD-Related HCC: Could Conventional and Doppler US Differentiate between Focal Liver Lesions (FLLs)?

According to multiple guidelines, B-mode US is the primary imaging technique used for HCC screening in high-risk patients [19,43]. Although B-mode US cannot make a final diagnosis, the main goal is to detect any focal area differing from the background parenchyma. The method represents a milestone in selecting further management, being suggestive when a tumor displays signs of malignancy. Therefore, any suspicion of malignancy should be considered a positive result of the ultrasound exam, and further evaluation of the lesion will need to establish a specific diagnosis [44].

The US Liver Imaging Reporting and Data System (LI-RADS) score was established by the American College of Radiology (ACR) as an algorithm for the evaluation and management of FLLs in order to improve high-risk patient care [45]. According to the LI-RADS algorithm, the size threshold determines the further path to diagnosis. Lesions measuring less than 1 cm are difficult to assess with certainty, regardless of the imaging method. Nevertheless, they are usually benign and require follow-up at 3–4 months. If the tumor remains unchanged after 2 years of surveillance, malignancy is excluded [19,43,46]. For larger lesions, the US findings are inconsistent and an in-depth characterization is mandatory. Malignancy suspicion is raised by large focal lesions with heterogeneous echostructure and signs of parenchymal distortion—defined as ill-defined area of heterogeneity, refractive edge shadowing, and distortion of the normal internal hepatic architecture [47]. HCC of any size shows variable echogenicity, but as it develops, the tumor might undergo fatty metamorphosis, leading to a hyperechoic structure and a higher risk of being confused with a hemangioma [48]. Another important finding is a new thrombus identified in the liver venous system, more frequently within the portal veins, which can represent a bland thrombus or tumor and strongly indicates a diagnosis of HCC [45,49].

In addition, US Doppler assessment of blood flow and vascularization is useful, but not definitive (Figure 2) [48,50]. Central or peritumoral hypervascularity, basket pattern (vascular network at the periphery of tumor penetrating to the center) and the presence of pulsatile afferent flow signal with constant efferent flow are typical findings suggestive of HCC [50,51]. Moreover, spectral Doppler analysis offers parameters such as maximum flow velocity (Vmax) and pulsatility index (PI), which are useful in the differential diagnosis of several hepatic tumors. Notably, a very high value of the PI is suggestive for HCC, increasing the diagnostic efficacy of ultrasonic methods [47,52].

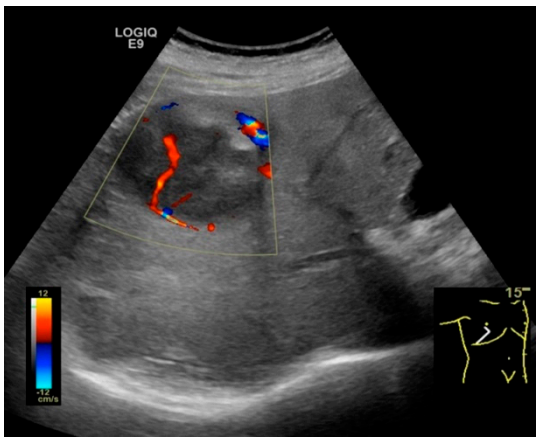


Figure 2. Hepatic steatosis. Focal liver lesion. 2D-US scan shows an enlarged liver with increased echogenicity and posterior beam attenuation. In addition, a focal parenchymal structure is observed in the right lobe. It is characterized as having decreased, heterogeneous echogenicity and internal vessels seen at Doppler examination. The diagnosis of the focal lesion remains uncertain and CEUS examination is necessary.

In NAFLD subjects, a notable confounder is represented by focal fatty sparing areas. However, lesions with typical location and shapes, as previously mentioned, and without mass effect, are suggestive ultrasonographic features for FFS [53]. Moreover, one study implied that FFS usually do not develop on previously homogeneous NAFLD, implying that a new ultrasonographic observation should be compared to former US examinations [54]. US Doppler comes as an adjuvant tool for conventional US. Usually, FFS are not hypervascular and do not distort the normal hepatic vessels. Nevertheless, the final diagnosis requires further imaging modalities, including contrast enhanced US (CEUS), computed tomography (CT), magnetic resonance imaging (MRI), or even US-guided biopsy [55].

Of note is a 2018 meta-analysis conducted by Tzartzeva et al. [56] that found an all stage pooled sensitivity for HCC detection of 84% with US, approximately equal to the CT/MRI sensitivities. In the same study, sensitivity for early-stage HCC was only 47% with US and 63% when combined with alpha-fetoprotein level (AFP), proving the limited use of US for small tumor detection. In addition, US findings are not specific, as appearances of FLLs overlap [48,57]. US allows accurate diagnosis for few FLLs, of which hemangioma, simple cyst, and calcifications are the most common [49]. In the same manner, US Doppler is limited in the diagnosis of focal nodular hyperplasia (FNH), in which the central artery traversing the central scar and its radial distribution are evocative in 80% of cases [53]. Concluding, most FLLs require a definitive characterization with a diagnostic multiphase contrast-enhanced examination (CEUS, CT or MRI).

3. Contrast-Enhanced Ultrasonography (CEUS): An Add-on to the Diagnostic Power of Ultrasonography in NAFLD-Related HCC

3.1. General and Technical Considerations

Contrast-enhanced ultrasonography (CEUS) is a particular US technique that overcame several drawbacks of both the conventional B-mode and Doppler ultrasound techniques by adding the intravenous administration of microbubble contrast agents [58,59]. When analyzing the liver, CEUS provides real-time recording and interpretation of the ultrasound contrast agent (UCA) flow through the parenchyma. Dynamic contrast-enhanced ultrasound (DCE-US) has made quantitative assessment possible and readily available by analyzing the time intensity curve (TIC) and facilitating measurement of the blood flow parameters [60].

Currently, there are four Food and Drug Administration (FDA)-approved UCAs available worldwide: SonoVue/Lumason (Bracco Suisse SA, Geneva, Switzerland), Definity/Luminity (Lantheus Medical Imaging, Inc., North Billerica, MA, USA), Optison, and Sonazoid (GE Healthcare AS, Oslo, Norway) [61]. These UCAs consist of biodegradable gas microbubbles, equal or smaller in size than red blood cells, stabilized in a phospholipid or albumin shell [58,59]. Because of their physical size, all UCAs act as blood pool agents, allowing the representation of both small and large vessels [62]. While SonoVue, Definity and Optison are purely intravascular agents, Sonazoid is phagocytosed by the hepatic reticuloendothelial cells (Kupffer cells). This leads to increased clearance from the vascular distribution volume and significant persistence in the liver, termed the post-vascular phase (also known as the Kupffer cell phase). Regardless of whether microbubbles are within the reticuloendothelial system or utterly within the blood pool, they can be easily destroyed by the ultrasound energy emitted by the examiner, providing real-time visualization of different vascular phases [60]. Given the dual blood supply of the liver, from the hepatic artery and the portal vein (25–30% and 70–75% of the total blood supply respectively), three different vascular phases have been defined: the arterial (AP), portal venous (PVP), and the late (LP) phase [61].

Moreover, UCAs enable the characterization of the vascular architecture through the phase-specific contrast enhancement in comparison to the background liver parenchyma. These characteristics are highly suggestive diagnostic features for various FLLs [60,61]. However, it is mandatory to perform a thorough B-mode and color Doppler US evaluation of the liver beforehand, considering that cysts and calcifications can be easily misinterpreted due to complete absence of enhancement. In addition, the assessment of

the underlying parenchyma is paramount in order to ascertain whether cirrhosis is present or not, which can be a game changer [61].

Indications, Advantages and Limitations of CEUS Compared to Conventional US

Currently, clinical practice guidelines recommend abdominal US surveillance for malignancy every 6 months among cirrhotic patients [19,43]. However, the detection of small HCC nodules is difficult in subjects with liver cirrhosis, since they usually present a coarse parenchyma [63]. In addition, a high percentage of NAFLD-related HCC cases arise on non-cirrhotic liver [64]. As previously mentioned, steatosis and obesity independently impair US sensitivity in NAFLD patients [17]. CEUS improves the accuracy of B-mode US, by adding a new dimension to the equation—it evaluates the enhancement properties and vascular architecture of FLLs as compared to the background parenchyma [59]. In an experimental NASH rat model, Carvalho et al. [65] reported increased sensitivity and specificity (71% and 96%, respectively) after contrast administration, compared to Doppler US (29% and 71%, respectively). For integrative purposes, we decided to summarize the indications, advantages, and limitations of the conventional US compared to CEUS in Table 2.

Table 2. Indications, advantages, and limitations of CEUS as compared to B-mode and Doppler US.

	Conventional B-Mode and Doppler Ultrasound	Contrast Enhanced Ultrasound (CEUS)
Indications	HCC surveillance for high risk patients [19,43] Guides biopsy or treatment [66]	Evaluates nodules $\geq$ 10 mm observed at US surveillance [59] Guides biopsy or treatment for observations that are undetectable or inconspicuous on US [59,61] Selects the most relevant lesion/lesion component for biopsy [59,61] Evaluates lesions with inconclusive histology [59] Better characterization of arterial phase enhancement in inconclusive CT/MRI [59] Differentiates between benign and malignant portal vein thrombosis [59,61] First line contrast imaging modality in patients with renal insufficiency [61]
Advantages	Broadly available [20] Free from ionizing radiation [21] Cost-effective Non-invasive Typical HCC features of Doppler findings are available [50] The wide variety of Doppler methods (color/spectral/power Doppler) for better assessment of FLLs [47,67]	UCAs are safe in adult and pediatric individuals [61] The possibility of re-administration of UCAs for better assessment of suspicious observations [61] Avoids unnecessary further imaging for benign lesions [59] Absence of ionizing radiation [68] Real-time and quantitative assessment [61] Cost-effective [69,70] Excludes pseudovascular lesions detected on CT or MRI such as arterioportal shunts [71]
Limitations	Low sensitivity in patients with morbid obesity [41] Steatosis leads to acoustic beam attenuation [36,72] Unable to differentiate between simple steatosis and progressive NASH [38,39] Unable to differentiate between steatosis and fibrosis [37] Inadequate to assess with certainty the degree of fatty infiltration [30] Focal fatty deposition or sparing areas can lead to confusion with other FLLs [35] Low sensitivity for early-stage HCC [56] Overlap of FLL appearance on the US image [57]	Unsuitable for HCC staging [60] Subdiaphragmatic or deep lesions are difficult to reach and characterize properly [59] Limited penetration in obese patients [59] Severe hepatic steatosis alters signal transmission through the parenchyma [59]

3.2. Assessment of Fatty Liver Progression Using CEUS

Studies evaluating chronic liver diseases using CEUS are rather scarce. However, fat accumulation is the key factor that leads to vascular impairment and increased vascular resistance. Technologies such as CEUS can appraise hepatic microcirculation and quantify early changes in the parenchymal flow, before the onset of fibrosis [73,74]. There are several in vivo studies that evaluated fatty liver progression and HCC development using untargeted CEUS [65,75,76]. Of note is the Pandit study [75] that identified disease progression using vascular parameters, concluding that NASH liver parenchyma has the lowest blood flow. On the other hand, Tsujimoto et al. [76] evaluated Kupffer cells dynamic and phagocytic activity in a rat NASH model using Levovist and observed a reduced contrast effect in the liver. In humans, several studies using transit time parameters, such as the hepatic vein transit time (HVTT), evaluated fibrosis in different chronic liver diseases including NAFLD, chronic hepatitis B, and chronic hepatitis C. They observed earlier arrival time of contrast agents in the hepatic veins in severe fibrotic patients, compared to their healthy counterparts, and concluded that intrahepatic hemodynamic changes, such as shunts or liver arterialization, play an important role in these changes [77–80]. To summarize, Table 3 embodies an overview of different techniques for fatty liver assessment.

Table 3. Characteristic of NAFLD by different non-invasive methods.

Technique	Features
B-mode US	Hepatomegaly Bright, hyperechoic liver compared to the right kidney Posterior beam attenuation Difficult visualization of echogenic structure, such as the portal vein wall, the gallbladder, the diaphragm etc.
Doppler US	Abnormal waveforms of the hepatic veins (normal triphasic pattern disappears) [81] Velocity of the portal flow (flow peak maximum velocity and mean flow velocity) and the portal vein pulsatility index (VPI) are significantly lower in patients with fatty liver when compared to the controls; it also corelates with the severity of the fatty liver [82]
US elastography	Fibrosis assessment by means of hepatic stiffness measurement Steatosis evaluation by the instrumentality of the Controlled Attenuation Parameter (CAP) [14]
CEUS	Earlier arrival time of contrast agents in hepatic veins using the hepatic vein transit time (HVTT) Reduced contrast effect in the Kupffer cell phase

3.3. The Evaluation of FLLs, Including HCC, in NAFLD Patients Using CEUS

Over the years, international guidelines sought to elucidate the role of CEUS for FLLs evaluation. At first, CEUS was considered an inappropriate diagnostic tool for HCC surveillance, and more expensive technologies, such as Contrast Enhanced CT (CeCT) or Contrast Enhanced MRI (CeMRI), were preferred [83,84]. However, in the past years, additional evidence has been published for all UCAs and proved otherwise [61]. The DEGUM multicenter trial [85–87], together with the multicenter study of Sporea et al. [88], showed that CEUS possesses powerful capacity in differentiating between malignant versus benign FLLs, as exemplified in Table 4. CEUS sensitivity ranges from 80–94% for all size focal lesions and 55–76% for those ≤20 mm, and the specificity from 82–98% for all size liver nodules and 80–98% for those ≤20 mm, providing similar performance to CT and MRI for characterizing FLLs [86,88,89]. Having 63–76% sensitivity and 87–98% specificity, CT enables full cross-sectional evaluation of the liver and provides staging information. Gadolinium-enhanced MRI offers a better depiction of intrinsic tumor characteristics than CT with 67–82% sensitivity and 86–94% specificity. Moreover, Gadoxetate-enhanced MRI is very sensitive for early and small lesions (≤20 mm) with 90–93% sensitivity and 87–91% specificity, facilitating the differentiation of early HCCs from cirrhosis-associated benign nodules. Functional MRI techniques, including diffusion-weighted imaging, MRI with hepatobiliary contrast agents, perfusion imaging, and magnetic resonance elastography are promising in providing additional imaging features for tumor microvascular invasion and growth patterns, allowing preoperative

prediction and prognosis [90]. Emerging as the most accurate and cost-effective imaging modality for FLLs characterization, CEUS is currently recommended as the first-line method for hepatic lesions evaluation, especially in patients with inconclusive CT or MRI findings, or among those with contraindications for these techniques [61]. In addition, recent analyses reported that Sonazoid CEUS surveillance might be a cost-effective method to increase expected survival time among at-risk subjects [67,91]. However, routine use of CEUS for HCC screening among patients at risk is currently not recommended and further research is needed to find ways to integrate such technologies into the healthcare surveillance strategies [61].

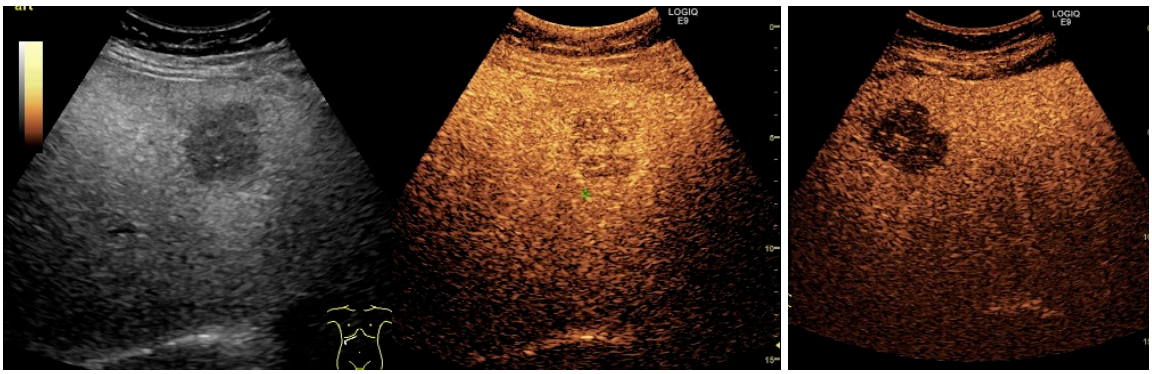
Table 4. CEUS capacity using different contrast agents (SonoVue, Sonazoid, Levovist) for differentiating between malignant versus benign FLLs.

Study	UCA Used	AUROC	Malignant Lesions				Benign Lesions					
			HCC		Metastases		Hemangioma		FNH		Hepatocellular Adenoma	
			Se (%)	Sp (%)	Se (%)	Sp (%)	Se (%)	Sp (%)	Se (%)	Sp (%)	Se (%)	Sp (%)
Auer et al. [92]	SonoVue	0.951	100 (*n* = 7)	100	90 (*n* = 31)	100	99 (*n* = 74)	100	100 (*n* = 19)	100	66.6 (*n* = 3)	100
Sawatzki et al. [93] [1]	SonoVue	N/S	Se = 96–97.2 [#] (*n* = 37)						Sp = 84.2–90.6 [#] (*n* = 75)			
Zhang et al. [94] *	SonoVue Sonazoid Levovist	0.94	85 (N/S)	91	N/S							
Yue et al. [95] [2]	SonoVue	0.70	Se = 72; Sp = 84.6 (*n* = 30)		(*n* = 30)							
Deng et al. [96] *	Sonazoid Levovist	0.93	86 (*n* = 30–104)	87	N/S							
Sporea et al. [88]	SonoVue	N/S	81.2 (*n* = 209)	94.2	93.1 (*n* = 109)	94.1	90.2 (*n* = 102)	97.6	94.7 (*n* = 19)	98.4	N/S (*n* = 7)	
Friedrich-Rust et al. [68] *	SonoVue Sonazoid Levovist	N/S	88 (*n* = 2238)	N/S	91 (*n* = 1775)	N/S	86 (*n* = 1191)	N/S	88 (*n* = 602)	N/S	N/S (*n* = 84)	
Xie et al. [97] *	SonoVue Levovist	0.9555	N/S									
Strobel et al. [86]	SonoVue	N/S	Se = 93.5 [#] (*n* = 154)						Sp = 66.7 [#] (*n* = 87)			
Seitz et al. [85] **	SonoVue	N/S	86.1 (*n* = 7/40 **)	96.6	93.6 (*n* = 7/56 **)	82.4	62.5 (*n* = 48/9 **)	97.3	57.1 (*n* = 31/14 **)	99.3	N/S	

* meta-analysis, ** The Seitz study used two subgroups defined as subgroup A—without histological verification/subgroup B—with histological verification, *n* = number of patients taken into consideration, N/S = not specified, [#] these studies evaluate CEUS ability to identify malignant FLLs from benign ones without further classification; [1] This study included 2 NAFLD/NASH patients and 32 cirrhotic patients, but did not use the CEUS LI-RADS algorithm; [2] This study used parametric imaging CEUS, differentiating between HCC and metastatic liver cancer using quantitative parameters.

3.3.1. Diagnostic Features of Hepatocellular Carcinoma on CEUS

The major features for HCC diagnosis on CEUS are arterial phase hyperenhancement followed by mild washout with late onset in the portal and/or late phase, as depicted in Figure 3 [59,98]. However, studies demonstrated that the enhancement patterns largely depend on the degree of arterial vascularization and the differentiation grade of the tumor [99,100]. In regards to the vascularization, studies reported arterial phase hyperenhancement in 90–97.8% of HCC lesions while hypoenhanced observations were mainly well differentiated HCCs [87,98,100,101]. In spite of that, Von Herbay et al. [102] reported 28% non-hyperenhanced HCC nodules. These results might be explained by the inclusion of undifferentiated (G4) HCC nodules, considered by Yang et al. [98] as FLLs with decreased arterial supply. Regarding the diameter of the FLL, the Von Herbay study found a significantly higher incidence (95%) of hypervascularization in larger (>3 cm), well differentiated (G1) HCC lesions, in comparison to smaller (<3 cm) G1 HCCs (43%) [102].



(**a**) (**b**) (**c**)

Figure 3. Hepatic steatosis. HCC. Conventional B-mode image (**a**), CEUS in the arterial phase (**b**), and CEUS in the late phase (**c**). The examination shows an enlarged liver with markedly increased echogenicity and a focal parenchymal lesion with decreased echogenicity (**a**). At CEUS technique, the lesion shows enhancement in the arterial phase (**b**), followed by washout in the late phase (**c**).

Mechanistically, the relationship between washout patterns and cellular differentiation is influenced by the amount of portal veins in the suspected nodule. In the multistep hepatocarcinogenesis, the supplying vessels undergo major changes, with normal arteries and portal veins decreasing, while the abnormal neoplastic arteries increase [103]. Therefore, HCC with poorer grades of differentiation tend to present moderate washout, whereas well differentiated HCCs are likely to be iso-enhancing in the LP [99,100,104]. Another key feature for HCC evaluation consists of proper assessment of washout chronology. As a real-time imaging technique, CEUS enables precise assessment of washout onset, a fundamental characteristic for the CEUS LI-RADS classification. HCC typically shows washout with late onset (>60 s), while non-hepatocellular lesions, including intrahepatic cholangiocarcinoma (ICC), present early washout onset (<60 s) [59].

The combined appraisal of the aforementioned diagnostic features makes it possible to evaluate the FLLs as malignant or benign in patients without underlying cirrhosis [87]. In those with liver cirrhosis and other risk factors for HCC development, CEUS can detect and characterize FLLs according to the LI-RADS classification. Released in 2016, CEUS LI-RADS is a standardized algorithm that classifies observations from LR-1 (a definitely benign lesion) to LR5 (an undoubtedly HCC). The LR score spectrum is illustrated in Figure 4. This table includes only CEUS pure blood pool agents (SonoVue, Luminity) [59,105–108]. A novel system proposed by Schellhaas et al. [109] redefined the population at risk for HCC, including patients with NASH and chronic hepatitis C with advanced fibrosis together with other key differences from the official CEUS LI-RADS. Nonetheless, their proposal was considered misleading by the ACR and consequently denied [110].

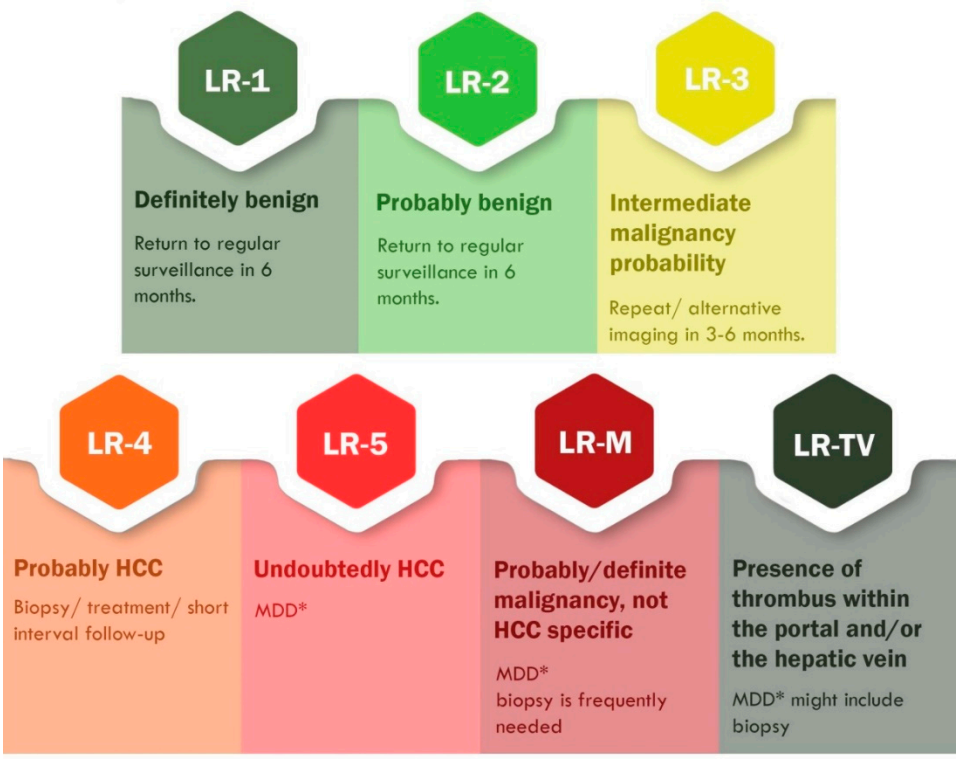


Figure 4. CEUS LI-RADS classification and management of FLLs according to the American College of Radiology [59,111]. This table includes only CEUS pure blood pool agents (SonoVue, Luminity). * MDD: multidisciplinary discussion; #MDD should be considered, since a recent prospective study found that 60% of CEUS LR-3 observations were HCCs [112].

3.3.2. HCC Particularities in NAFLD Patients

FLLs are frequent findings in clinical practice in patients with chronic liver diseases, such as cirrhosis or steatosis. One important aspect of HCC among NAFLD subjects remains its arduous detection. This is mainly due to subcutaneous fatty accumulation in addition to hepatic steatosis, which may alter the US visualization of small or early stage HCC nodules. Therefore, screening among these individuals remains controversial due to low cost-effectiveness. However, the recent study by Harris et al. [113] emphasized that screening among obese and NAFLD patients is of great interest and that clinicians should consider alternative imaging methods if US is limited.

Another important aspect among NAFLD patients remains the wide variety of differential diagnosis. In particular, focal fatty changes, either by fat depositions or fatty sparing, may also occur, impairing the diagnostic accuracy of B-mode US examination. However, an iso-enhancing observation during all phases, without washout on CEUS, enables proper diagnosis, without the need for further imaging (Figure 5) [59,114]. Also, several studies aimed to elucidate whether underlying hepatic condition may alter lesions enhancement patterns. Yang et al. [98] reported no significant difference on the dynamic enhancement of HCC using CEUS in patients with or without cirrhosis.

3.3.3. Sonazoid-Enhanced US—A Breakthrough in the CEUS Practice

As mentioned beforehand, Sonazoid accumulates in the reticuloendothelial system. Moreover, Sonazoid-enhanced US facilitates FLLs characterization, histological grading and guided percutaneous ablation therapy [115,116]. It is well-known that macrophages play an important role in malignancies [117]; Kupffer cells are specialized macrophages localized within the lumen of the liver sinusoid; the absence of these Kupffer cells in poorly differentiated HCCs usually causes contrast defect, corresponding to hypo-enhancement in the post vascular phase [58]. Nonetheless, in the Arita study [118], half of the well differentiated HCCs did not show lacking enhancement in the Kupffer cell phase. Recently,

a meta-analysis by Wu et al. [119] found that Sonazoid has the highest diagnostic accuracy among all UCAs. However, being available only in Japan, South Korea, and Norway so far, only four studies were included in the Wu meta-analysis. Therefore, further worldwide research is needed in order to integrate Kupffer cell agents in the CEUS LI-RADS algorithm for FLLs characterization, considering the large palette of advantages that this method could bring to the clinician [105].

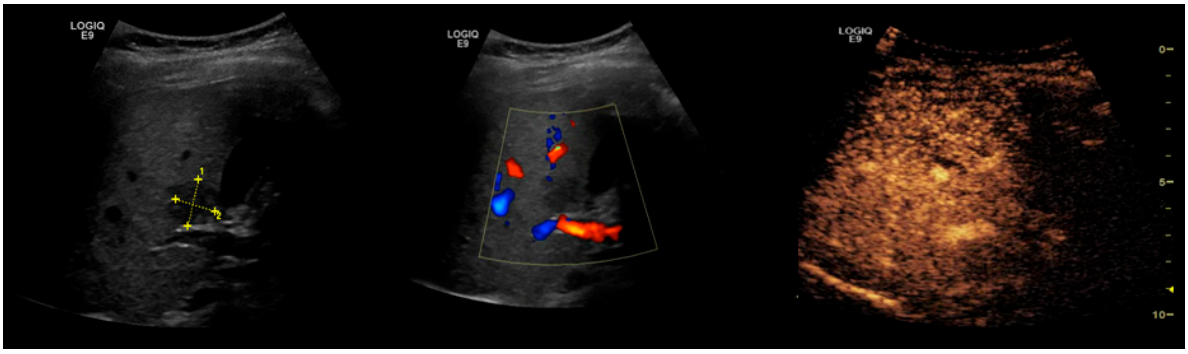


Figure 5. Focal sparing in the pericholecystic region. Hypoechoic image located around the gallbladder in a fatty liver. The Doppler examination cannot reveal any vessels within the lesion. On CEUS, the enhancement was homogeneous during the arterial, portal, and parenchymal phases, without any apparent focal lesions.

4. Artificial Intelligence in the Ultrasonographic Evaluation of NAFLD and NAFLD-Related HCC: A Potential Pillar

Ultrasound imaging is a widely used technique in today's clinical practice. It provides both qualitative and quantitative information in a non-invasive manner, which benefits the patient. The classic examination performed by the radiologist/radiographer is operator-dependent, subjective, and cannot differentiate between steatosis and fibrosis; furthermore, conventional B-mode US is not able to establish the exact amount of fat accumulation in the hepatocytes. Artificial intelligence could revolutionize the evaluation of the images through a detailed and comprehensive analysis. Computerized image analysis can detect different textures from the ultrasound acquisitions, based on the physical and architectural alterations that affect the propagation of US waves. The use of computers in US image analysis started several years ago with the introduction of methods like grayscale analysis, ultrasound histogram, attenuation and/or texture information, and computer-assisted quantitative analysis of ultrasound beam echo amplitude [120–122]. Another method that can appraise steatosis severity is the computerized calculation of the hepatorenal ratio, with a sensibility of 91.3% and a specificity of 83% if the hepato-renal difference is $\geq$7 dB [30]. However, the efficacy of these rudimentary computerized methods remains questionable and the progress towards the applications of artificial intelligence is within our grasp.

In the past years, artificial intelligence (AI)-based methods, especially deep learning (DL) algorithms, gained extensive attention in the field of ultrasound imaging. In broad terms, we highlight two AI techniques with applications within the imaging field—machine learning (ML)-based algorithms with its more advanced class of DL. Convolutional neural networks (CNNs) are the most popular DL architecture used in medical imaging, although they require large amounts of training data [123,124]. AI-based algorithms that guide the examiner towards the best image acquiring position have been developed, so that, in the future, the examiner will not necessarily need to have previous US technique knowledge. In the near future, DL algorithms may provide accurate interpretation of various US images acquired by the examiner while returning a probable imaging diagnosis [125], assisting the physician in completing the clinical diagnosis and prioritizing urgent cases based on entities identified in the scans [126]. This section aims to discuss the current state of the AI research in the US evaluation of NAFLD and NAFLD-related HCC, focusing on the clinical applications of AI-based methods rather than the technology behind it.

Radiomics emerged as a new method in improving the accuracy of the clinical decision making based on medical imaging reports. It refers to the high-throughput mining of data from medical imaging. In general terms, the workflow of radiomics begins with the first step referring to the acquisition of standardized images, followed by the segmentation of the entities present within the image (either automatically, or by the physician) in order to define the desired region of exploration. Next, quantitative features, such as intensity levels, texture pattern, shapes, and the spatial interrelation of different entities are retrieved from the selected region with a consequent analysis based on complex algorithms. The most prominent data are investigated in relationship with treatment and prognosis, the main goal being accurate risk stratification [127–129].

From a brief technical perspective, the goal of the machine learning (ML) techniques is to study the underlying US features and transform them into information for segmentation or classification [130]. Furthermore, ML methods can be supervised and unsupervised; in supervised ML algorithms, the classifier is trained on an existing database containing US images that are labeled with the required outputs. Contrarily, unsupervised learning algorithms identify similarities in the input data, with no labels provided [131].

DL methods are a subclass of machine learning algorithms in computer science [130]. In the learning phase of DL algorithms, the labeled US images are randomly divided into two separate groups—training and validation; images from within the training group are used to automatically identify features and a specific model learned. Next, the validation group is used in order to estimate the performance of the best learned model identified. The DL algorithm will then be able to apply the learned algorithm to analyze a new US image and to make predictions. [131]. CNNs are the most popular DL architecture used in medical imaging and are inspired from the biologic neural networks, containing multiple computational units entitled artificial neurons that analyze the input images [132].

An unsupervised neural network that is worth mentioning is represented by stacked autoencoders. Briefly, these algorithms learns the representation of the input data by attempting to reconstruct it [130].

4.1. The Applications of AI in the Ultrasonographic Evaluation of NAFLD

As mentioned beforehand, the gold standard for NAFLD diagnosis is biopsy, but its invasiveness severely limits the method to specialized healthcare units. Currently, US is an invaluable non-invasive technique in the first-line examination of patients with clinical suspicion of NAFLD. Although a number of studies have tried to standardize a grading system for the US evaluation of NAFLD, all criteria still remain subjective. Considering that the Hernaez meta-analysis found a 84.8% sensitivity and a 93.6% specificity for detection of moderate and severe steatosis, whilst mild steatosis had considerably lower sensitivity [22], we sought to determine whether AI could potentially improve the US detectability of NAFLD.

A study by Han et al. [133] sought to evaluate DL algorithms that use radiofrequency (RF) data for NAFLD evaluation, analyzing 204 participants with 140 NAFLD-affected patients. Reference was set with MRI-derived proton density fat fraction (PDFF). Two one-dimensional CNN algorithms were developed—a binary classifier and a fat fraction estimator. Furthermore, the Han study divided participants into training group (n = 102) and test group (n = 102) by stratified randomization. The CNN algorithms were then developed through cross-validation, using the training group, and further evaluated in the test group. The Han study showed a high classification accuracy classifier (96%) with an AUROC of 0.98. Moreover, the sensitivity in the RF without time gain compensation was 97% [95% CI: 90–100%] and specificity 94% [95% CI: 79–99%] [133].

Furthermore, in a study by Biswas et al. [134] that included 63 patients, the accuracy, sensitivity and specificity for detecting fatty liver disease and making the risk stratification based on deep learning ultrasound (US) was 100%. The AUROC of deep learning method was 1.0 compared to extreme learning machine, which had an AUROC of 0.9222, sensitivity of 93.33% and specificity of 90.83%; support vector machines (SVM) had an AUROC of

0.8208, average sensitivity of 64.21%, and specificity of 93.56%, highlighting the better performances of deep learning technology in this study. Another study by Byra et al. [135] proposed the use of a CNN model for liver steatosis assessment in B-mode ultrasound imaging. Their work included 55 severe obese patients, 38 of whom had fatty liver disease. The overall result was significantly better than conventional B-mode US, with an AUROC of 0.977, accuracy of 96.3%, sensitivity of 100% and specificity of 88.2%, whereas the accuracy when using the hepatorenal index was 90.9% and the accuracy of gray-level co-occurrence algorithm was 85.4%. The Cao study [136] recruited 240 patients from routine abdominal US examinations and compared the performance of envelope signal value, gray scale value, and deep learning in diagnosing NAFLD, as well as differentiating between mild, moderate, and severe steatosis. The DL index did not follow a Gaussian distribution, but presented obvious differences between the mild, moderate, and severe NAFLD groups. In the Cao study, in terms of diagnosing NAFLD, deep learning-based algorithm had the best performance, with the highest DL index and an AUROC of 0.933, compared to gray scale value (AUROC = 0.857) and envelope signal (AUROC = 0.859). Whilst all three methods showed poor diagnostic capability in terms of NAFLD scoring between mild and moderate NAFLD (AUROC < 0.7), DL index showed much better capability (AUROC = 0.958) in distinguishing between moderate and severe NAFLD [136]. As such, the existing data within the literature suggests that deep learning methods can be a viable addition to the current clinical practice in diagnosing NAFLD. However, further studies are required in order to standardize this approach.

4.2. The Applications of AI in the Ultrasonographic Evaluation of NAFLD-Related HCC

The clinical day-to-day life proved that there is a need to detect HCC in early stages, but the current limitations regarding imaging techniques hamper the early diagnosis of this malignancy. AI is constantly and steadily evolving and could become an important player in early detection and staging. For comprehensibility purposes, Table 5 presents a brief overview upon the latest studies involving the potential of AI in the US detection of HCC and NAFLD-related HCC.

Table 5. A brief overview upon a selection of recent studies that evaluate the potential of AI techniques in the detection of HCC and NAFLD-related HCC.

Study	AI Technical Considerations	Accuracy of the AI Method
Bharti et al. [137]	Deep learning	Detection of • Normal liver (n = 24 patients): Se/Sp = 96.3%/99.2% • CLD (n = 25 patients): Se/Sp = 95.5%/98.0% • Cirrhotic liver (n = 25 patients): Se/Sp = 97.5%/98.2% • HCC on a cirrhotic liver (n = 20 patients): Se/Sp = 96.9%/99.8%
Hassan et al. [138]	Deep learning	Detection of HCCs, liver cysts and hemangiomas • Se/Sp for the classification performance: 98.0%/95.7% • Overall accuracy: 97.2%
Sato et al. [139]	Machine learning	Prediction of HCC (n = 539 patients with HCC, n = 1043 patients without HCC) • Se/Sp = 93.27%/75.93% • AUC = 0.940
Schmauch et al. [140]	Deep learning	Detection and characterization of FLL (benign vs. malignant) Training (n = 367 patients): • Detection AUROC = 0.935 • Characterization AUROC = 0.916 Test (n = 177 patients): • AUROC = 0.891 for 7 different tasks

Taking into consideration all the aforementioned studies, our opinion is that AI can dramatically improve the US detection of NAFLD and NAFLD-associated pathological entities, such as cirrhosis and HCC, through DL algorithms.

4.3. Advantages and Pitfalls of Future AI-Based Solutions

AI techniques present a number of advantages when they are employed. The diagnostic accuracy of a number of pathologies can greatly increase, which can be translated into a better patient survival in the case of early HCC detection. Our paper has identified recent studies that demonstrate the wide potential of DL algorithms in identifying NAFLD and NAFLD-related HCC [141]. We also highlight the increase in productivity and the improvement in the clinical decision making, which essentially translates in better patient satisfaction.

However, there are different elements that can hinder the development of ML solutions and currently limit their applicability in US medical imaging. In order to achieve good learning performance with deep learning, there is a need for large sets of data during the training process from which the algorithms "learn", which may currently be unavailable. For the supervised methods, the experts would have to swift through massive datasets and manually add annotations for the specific task, posing a real question of how to train such a model in a cost-effective and time-effective manner. Furthermore, there are several US-related features that can hamper the learning power of the AI: the artifacts in B-mode liver ultrasound (e.g., acoustic enhancement, comet tail, mirror image) or in Doppler mode (such as aliasing phenomenon or blooming artifact) must be recognized and not mistakenly diagnosed by the computer as pathologic. On the other hand, the US parameters (gain-brightness, depth, TGC curve, field of view) and the selection of probes must also be taken into consideration. Therefore, because of the variables related to the US machine as well as to the patient, the need for standardization is vital in order to achieve good results.

Eventually, there are potential biases that need to be considered before integrating AI in clinical practice. In the "anchoring effect", the operator tends to make an interpretation in relation with the initial reference and can get biased in the decision making [142]. The second bias is one that could occur in systems based on supervised learning and is called the "bandwagon effect". Knowing that the automated decision is based on a large collection of annotations, the operators tend to position their opinion with the algorithm [143].

Even if the medical imaging could benefit from the developments in computer science, mainly CNN, there is still a need to standardize the evaluator potential in order to achieve the best possible results. The constant evolution of the automated systems shines a bright light towards the future of ultrasound imaging.

5. Concluding Remarks

The silent progression of NAFLD towards NAFLD-related HCC prompts for accurate disease-specific surveillance tools that present a high accuracy. Ultrasound-based methods are currently the epicenter of NAFLD evaluation, with B-mode US being the first-line examination in high clinical NAFLD suspicion patients.

US-based methods are a powerful addition to the clinical examination in NAFLD patients, providing qualitative, quantitative, or both qualitative–quantitative information in NAFLD, depending on the technique used. Conventional B-mode US is a broadly available, cost-effective, non-invasive method that returns only qualitative-subjective information and has a reported sensitivity of 85% and 95% specificity for detecting moderate to severe steatosis, but lacks accuracy in the evaluation of mild steatosis. Furthermore, conventional B-mode US can identify focal liver lesions, but cannot make an in-depth characterization; malignancy is suspected in large focal lesions with heterogeneous echostructure and signs of parenchymal distortion. Doppler blood flow evaluation can identify a central or peritumoral hypervascularity, basket pattern, or the presence of pulsatile afferent flow signal with a concomitant constant efferent flow, which are suggestive of HCC but not definitive. Although these US techniques

are not the first-line HCC diagnostic methods, they remain important first-line screening and surveillance tools. In regard to CEUS, the add-on of UCAs has rendered possible the further characterization of FLLs by adding a new real-time quantitative assessment into the equation. As an accurate and cost-effective imaging modality for hepatic lesion evaluation, CEUS provides the HCC diagnosis through the standardized LI-RADS score and the characteristic arterial phase hyperenhancement followed by mild washout with late onset in the portal/late phase. The use of the current UCAs and US contrast-specific techniques has brought CEUS to a similar performance to CT and MRI for the characterizing focal liver lesions. In addition, compared to dynamic CT and MRI, US can be performed in real time, is less expensive, and has no associated nephrotoxicity or ionizing radiation.

The current paper also underlines the wide potential of Artificial Intelligence-based methods, with a focus on deep learning algorithms, in the NAFLD and NAFLD-related HCC's US images analysis. The literature search has identified a number of studies focused on NAFLD and NAFLD-related HCC that prove an increase in the diagnostic accuracy of these methods, when deep learning methods are employed. Our opinion is that AI could potentially be a game changer that widens the power of US based methods and, finally, benefits the patient by the early detection of NAFLD-related HCC.

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cancers

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Review

Hepatocellular Carcinoma and Non-Alcoholic Fatty Liver Disease: A Step Forward for Better Evaluation Using Ultrasound Elastography

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Simple Summary: Non-alcoholic fatty liver disease (NAFLD) attracts a lot of attention, due to the increasing prevalence and progression to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Consequently, new non-invasive, cost-effective diagnostic methods are needed. This review aims to explore the diagnostic performance of ultrasound (US) elastography in NAFLD and NAFLD-related HCC, adding a new dimension to the conventional US examination—the liver stiffness quantification. The vibration controlled transient elastography (VCTE), and 2D-Shear wave elastography (2D-SWE) are effective in staging liver fibrosis in NAFLD. VCTE presents the upside of assessing steatosis through the controlled attenuation parameter. Hereby, we critically reviewed the elastography techniques for the quantitative characterization of focal liver lesions (FLLs), focusing on HCC: Point shear wave elastography and 2D-SWE. 2D-SWE presents a great potential to differentiate malignant from benign FLLs, guiding the clinician towards the next diagnostic steps. As a disease-specific surveillance tool, US elastography presents prognostic capability, improving the NAFLD-related HCC monitoring.

Abstract: The increasing prevalence of non-alcoholic fatty liver disease (NAFLD) in the general population prompts for a quick response from physicians. As NAFLD can progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC), new non-invasive, rapid, cost-effective diagnostic methods are needed. In this review, we explore the diagnostic performance of ultrasound elastography for non-invasive assessment of NAFLD and NAFLD-related HCC. Elastography provides a new dimension to the conventional ultrasound examination, by adding the liver stiffness quantification in the diagnostic algorithm. Whilst the most efficient elastographic techniques in staging liver fibrosis in NAFLD are vibration controlled transient elastography (VCTE) and 2D-Shear wave elastography (2D-SWE), VCTE presents the upside of assessing steatosis through the controlled attenuation parameter (CAP). Hereby, we have also critically reviewed the most important elastographic techniques for the quantitative characterization of focal liver lesions (FLLs), focusing on HCC: Point shear wave elastography (pSWE) and 2D-SWE. As our paper shows, elastography should not be considered as a substitute for FLL biopsy because of the stiffness values overlap. Furthermore, by using non-invasive, disease-specific surveillance tools, such as US elastography, a subset of the non-cirrhotic NAFLD patients at risk for developing HCC can be detected early, leading to a better outcome. A recent ultrasomics study exemplified the wide

potential of 2D-SWE to differentiate benign FLLs from malignant ones, guiding the clinician towards the next steps of diagnosis and contributing to better long-term disease surveillance.

Keywords: hepatocellular carcinoma; non-alcoholic fatty liver disease; ultrasound elastography; fibrosis; steatosis; focal liver lesion

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has become a major public health issue, with a current global prevalence estimated at around 25%, and a tendency of rapidly growing [1]. The spectrum of NAFLD varies from simple steatosis to non-alcoholic steatohepatitis (NASH), but further progression can lead to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). A meta-analysis that included worldwide studies from 1985 to 2005 estimated the HCC incidence among NAFLD patients at 0.44 per 1000 person-years (range 0.29–0.66). Furthermore, the incidence of HCC in NASH was even higher, estimated at 5.29 per 1000 person-years (range: 0.75–37.56) [1]. At first sight, the NAFLD-related HCC incidence is low; however, the rise of concerns is given by the increasing prevalence of obesity worldwide, precisely a twofold growth in the last 40 years [2]. The prognosis of NAFLD-related HCC is poor and curative interventions are often excluded because of the late diagnosis. The etiologies for HCC in liver transplant candidates showed a shift during the last years, with a decrease of hepatitis C virus (HCV) and alcohol etiologies and a higher percentage of NAFLD-related HCC [3,4]. This trend highlights the increasing importance of detecting early developing HCC in NAFLD patients through rapid, non-invasive means.

Current guidelines lack recommendations for surveillance of non-cirrhotic NAFLD/NASH patients who are at risk for developing HCC. In a United States population-based study, 54% of patients were found to have NAFLD-related HCC without underlying cirrhosis [5]. A study by Mittal et al. [6] found that the NAFLD patients are five times more likely to develop HCC in the absence of cirrhosis than HCV patients. Notably, most NAFLD patients included in this study suffered from obesity and diabetes, supporting the pathogenetic hypothesis. Despite the poor prognosis of NAFLD-related HCC, due to late diagnosis and curative interventions often excluded, the recommendation on HCC surveillance in patients without significant fibrosis is controversial because of its low cost-effectiveness [7].

At the moment, ultrasound (US) is the first-line imaging method used for the screening of liver cancer, but the technique encounters several limitations in NAFLD patients. A study that aimed to investigate the drawbacks of US when detecting HCC estimated a US sensitivity in obese patients of 76% versus 87% in non-obese patients ($p = 0.01$). The same study found a US sensitivity of 59% for NASH detection versus 84% in the case of other etiologies of liver disease ($p = 0.003$). These results illustrate that the body mass index (BMI) and steatosis itself represent two independent factors leading to an inadequate ultrasound image [8]. Moreover, computed tomography (CT) and magnetic resonance imaging (MRI) scans are not affected by these US limitations; however, because of the radiation exposure and the high cost, respectively, these techniques may not be an appropriate choice for initial surveillance. Furthermore, the imaging diagnostic criteria for HCC detection on CT and MRI should be used with great carefulness in patients with underlying NASH, since 40% of HCC nodules do not display wash-out on the portal or delayed phase images on MRI; encapsulation was identified only in 60% of HCC nodules, leading to difficult interpretation [9,10]. Therefore, these patients are more likely to require a liver biopsy, which is able to confirm de HCC and characterize the status of the liver parenchyma affected by NAFLD [11]. The procedure is indicated with caution, as it holds the potential for severe complications and sampling errors [12]. In this regard, every novel information provided by noninvasive methods of evaluation can help the clinician run an early and accurate diagnosis and reduce the number of liver biopsies.

Recently, the ultrasound elastography has received widespread attention by adding a new dimension to noninvasively, easily accessible methods of assessing liver diseases. All liver diseases,

focal and diffuse, are associated with changes in the structure of the tissue, with altered liver stiffness (LS), precisely the changes that elastographic techniques can detect and quantify. As such, this review aims to highlight the role of ultrasound elastographic techniques to assess both the focal liver lesions (FLLs) and the liver parenchyma status on which the FLL has developed.

2. Clinical Considerations: The HCC-NAFLD-NASH Trio

The spectrum of NAFLD varies from simple fatty liver, defined as triglyceride accumulation in more than 5% of the hepatocytes, to NASH, with the latter also including ballooning and lobular inflammation at the histological level. The NASH inflammatory state usually progresses with severe liver cell damage and subsequent fibrosis [13]. Concomitantly, NAFLD can progress with fibrosis as well. The further advancement of the disease can lead to serious consequences, such as compensated and decompensated cirrhosis and a higher risk of HCC [14]. We note that the NAFLD-related HCC can arise on both cirrhotic and non-cirrhotic livers, but a higher percentage has been reported in non-cirrhotic patients [5,15]. Figure 1 presents the main HCC etiologies, with a focus on NAFLD.

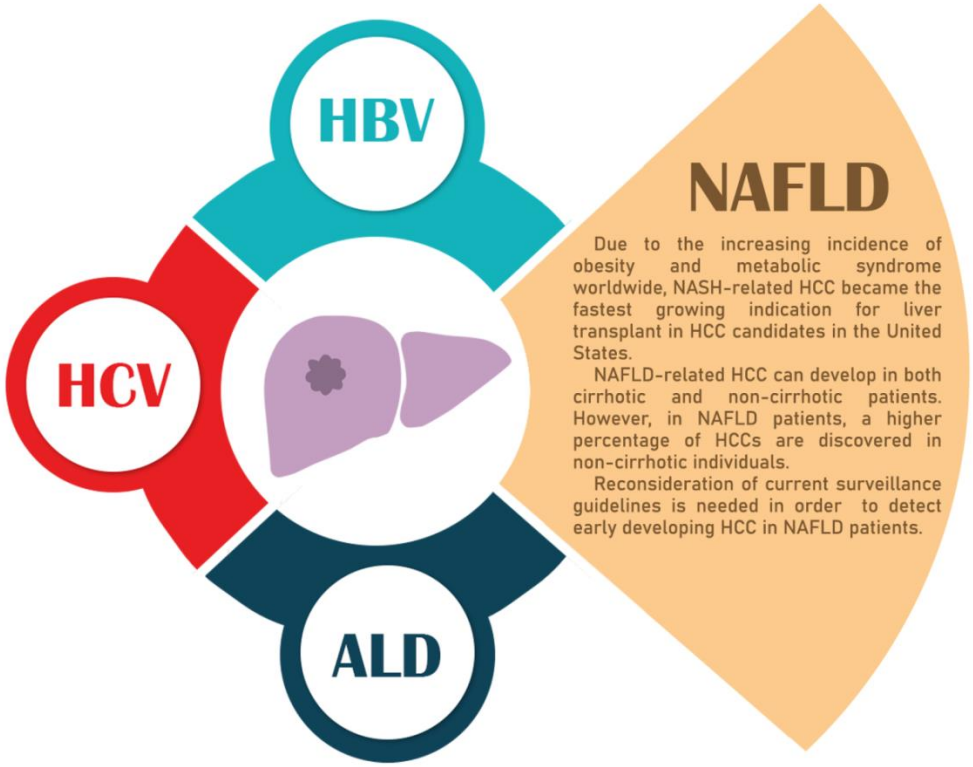

Figure 1. A graphical representation of the main hepatocellular carcinoma (HCC) etiologies. The main risk factors in HCC development are HBV, hepatitis C virus (HCV), alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). The increasing prevalence of NAFLD and its silent progression towards fibrosis, cirrhosis, and HCC requires new non-invasive diagnostic methods. NASH, non-alcoholic steatohepatitis.

The increasing incidence of obesity and metabolic syndrome (MetS), along with their hepatic involvement–NAFLD–led to a change in the etiology of HCC. Furthermore, the improvements in the prevention and treatment of hepatitis B virus (HBV) and the current effective curative treatment of HCV indicate this transition as well.

The liver oncogenesis in NAFLD/NASH is complex and multifactorial, involving lipotoxicity, intestinal microflora dysregulation with elevated levels of lipopolysaccharide (LPS), hyperinsulinemia with insulin resistance, increased IGF levels, and a low grade chronic systemic inflammatory response [16]. Genetic polymorphism and increased iron absorption may be contributing factors for the NASH-related HCC development [17]; oncogenic mechanisms, such as

telomere erosion, chromosome segregation defects, and alterations in the DNA-damage-response pathways, leading to genomic instability have been incriminated as well [18,19]. Kanwal et al. [20] reported that male sex, diabetes, and senior age are all independent risk factors for developing cancer. Additionally, Yang's novel study [21] found that low albumin significantly predicted the development of HCC; whereas, body mass index (BMI), hypertension, and hyperlipidemia did not. In comparison, the hepatocarcinogenesis in HBV and HCV infections are associated with the induction of chronic inflammation, along with molecular alterations that may induce mutagenesis in the case of HBV. The expression of viral proteins and the viral life cycle are other factors that drive the carcinogenesis in these patients [22].

Moreover, several studies illustrated the high risk of HCC in cirrhotic NAFLD patients; in this particular case, bi-annual ultrasound (US) surveillance is universally recommended [14,23]. However, there are no clear guidelines for cost-effective surveillance of non-cirrhotic NAFLD patients [24]. Furthermore, there is compelling evidence that NASH-related HCC patients receive less surveillance and treatment compared to patients with other HCC etiologies [25]. Although patients with NAFLD/NASH usually present less aggressive HCCs, the likelihood that they may be diagnosed by current monitoring is low, leading to late diagnosis and a poor prognosis [26–28].

Reconsideration of the current surveillance guidelines is needed [29], to increase the detectability rate of HCC in NAFLD patients at a screening level. Using new imaging techniques, such as US liver elastography, combined with non-invasive biomarkers, a subpopulation of the non-cirrhotic NAFLD patients carrying a clinical risk of HCC development could be identified, leading to increased and early HCC detectability [30].

3. The Main Elastographic Techniques

Historically, elastography drew inspiration from the diagnostic palpation, a clinical method used to determine the consistency of an organ or a lesion. This technique is based on the elastic properties of the material, the ability to regain its shape and dimensions after being the subject of a deforming force [31]. Therefore, elastographic methods involve applying mechanical stress on a tissue and evaluating its behavior.

The most notable elastographic techniques use ultrasound or magnetic resonance imaging (MRI). Magnetic resonance elastography (MRE) has several strengths compared to the ultrasound techniques. MRE generates a quantitive 3D elasticity map that covers an entire organ, it is less operator-dependent, and it is not limited by air or bone. However, when considering liver assessment, MRE has a rather limited utility compared to the ultrasound methods because of the high costs and the limited availability [32]. This review will focus on the role of ultrasound elastographic techniques, due to their larger accessibility and potential to detect focal liver lesions.

According to several elastography guidelines [33–35], the ultrasound elastographic techniques can be classified as either quantitative ("Shear Wave Elastography", SWE) or qualitative ("Strain Elastography"). The "strain" techniques are less used in the assessment of diffuse liver diseases. Currently, there are three main quantitative techniques used in clinical practice [35]:

- Vibration controlled transient elastography—VCTE (FibroScan®, Echosens, Paris, France)
- Point Shear wave elastography (ARFI-based technique): VTQ (Siemens Healthcare, Berlin, Germany), ElastPQ (Philips Healthcare, Amsterdam, The Netherlands), SWM (Hitachi Aloka Medical, Tokyo, Japan), QelaXto® (Esaote, Genoa, Italy), S-shearwave® (Samsung, Seoul, South Korea), STQ® (Mindray, Shenzhen, China)
- 2D-Shear wave elastography (ARFI-based technique): SSI (SuperSonic Imagine, Aixplorer®, Aix-en-Provence, France), ElastQ® (Philips, Healthcare, Amsterdam, The Netherlands), 2D-SWE.GE (GE Healthcare, Chicago, IL, USA), ToSWE (Toshiba Medical Systems, Tokyo, Japan), STE® (Mindray, Shenzhen, China)

3.1. Vibration Controlled Transient Elastography (VCTE)

VCTE is an elastographic technique that displays the shear wave velocity through the liver; the FibroScan device [34] consists of an ultrasonic transducer mounted at the end of an electrodynamic vibrator [36,37]. A single cycle of low-frequency vibrations (50 Hz) is applied at the surface of the body, producing a transient shear wave deformation, which propagates deeper in the liver parenchyma. The shear wave is tracked through multiple ultrasounds acquisitions, whilst the speed of the wave is calculated and used to deduct the Young modulus, according to the equation $E = 3\varrho Vs2$, where E is the Young or the elasticity modulus, ϱ is the density of the material (constant), and Vs2 is the velocity of the shear wave previously determined [32,38,39]. Young modulus, E, is measured in kilopascals (kPa), and it corresponds to the liver stiffness, such that a higher value indicates a stiffer tissue. Liver stiffness range between 1.5 to 75 kPa [40,41] with normal values at around 4.5 to 5.5 kPa in the healthy population [35]. The equipment displays the median of the measured Young's modulus, the interquartile range (IQR), the interquartile range/median ratio (IQR/M) after 10 conclusive measurements, and also the success rate of the measurements (SR) [31]. According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guideline, it is necessary to obtain 10 valid measurements with an IQR < 30% of the median value of the liver stiffness for a good test reliability [35].

One of the major drawbacks of VCTE is the low success rate among obese subjects [42]. Because of that, the manufacturer created a new XL probe destined to high BMI subjects that is able to increase the VCTE success rate. As such, the M probe is used for standard examinations, and the XL probe is designed to evaluate overweight patients. Using a lower frequency of 2.5 MHz, the XL probe allows liver stiffness measurement at a greater depth, being more reliable than the regular (M) probe when used in patients with BMI > 30 kg/m^2 [43–45].

Furthermore, VCTE is able to evaluate a predefined volume of approximately 1 cm wide per 4 cm long cylinder—at least 100 times the size of a biopsy sample. Consequently, the method not only makes a non-invasive assumption of the fibrosis and steatosis status, but the sample volume is considerably larger when compared to the standard biopsy [31].

Controlled Attenuation Parameter—A Novel Tool for Steatosis Assessment Using VCTE

The Controlled Attenuation Parameter (CAP) estimates the total ultrasonic attenuation and has been developed as a feature of the FibroScan® device for assessing liver steatosis [46,47]. CAP is evaluated using the same radiofrequency data, and the same region of interest as the region used to assess the LS. Therefore, the equipment can measure the liver stiffness (for the estimation of fibrosis) at the same time with CAP (for the estimation of steatosis) [39,43,46,48]. CAP is expressed in dB/m, ranging between 100 and 400 dB/m, with normal values under 247 dB/m [49]. As CAP was first implemented on the M probe, the add-on of CAP on the XL probe overcame the measurement failure acquired in 7.7% of cases when using the standard M probe in patients with increased BMI (>30 kg/m^2) [50]. Both probes have similar diagnostic performance, and recent studies have shown similar cut-offs when used accordingly to each patient's morphology [51–53].

3.2. Point Shear Wave Elastography (pSWE)

"Point SWE" is another category of elastographic techniques; our review will focus on the acoustic radiation force impulse (ARFI) technique (Siemens), since it is, to date, the only one that has been analyzed in the context of NAFLD patients. This quantitative technique provides a single uni-dimensional measurement of tissue elasticity, similar to FibroScan®. Furthermore, the 1 × 0.5 cm measurement area can be positioned by the evaluating physician on a two-dimensional bright-mode (B-mode) US image in any region of the hepatic parenchyma with no vasculature and to a maximum depth of 8 cm from the skin plane. Point shear wave elastography (pSWE) measures the shear wave velocity (SWV), in m/s, that was induced by the acoustic radiation propagating in the tissue [39,54–57]. The normal values range between 1.01 m/s and 1.59 m/s in healthy individuals [35].

3.3. Two-Dimensional SWE (2D-SWE)

"2D-SWE" is another category of US quantitative elastographic technique. Compared to the pSWE technology, which produces displacement in a single focal location, the 2D-SWE produces dynamic stress in multiple focal zones, using the same ARFI technique. The shear waves propagate laterally in the shape of a cone, and the ultrasound detection pulses provide acquisitions at a very high rate to detect the movement in real-time and to evaluate the SWV [31,35]. The Young's modulus (E) is determined by the equation $E = 3\varrho c^2$, where ϱ is the tissue density (constant), and c is the shear wave speed [35]. A colored map of the stiffness is created and is superimposed on the B-mode image of the ultrasound equipment, providing both anatomical (ultrasonic) and stiffness information. The quantitative assessment of the stiffness is also available, and the results are provided in kPa or m/s [58,59]. In healthy people, the Young's modulus varies between 4.5 to 5.5 kPa using the SuperSonic Imagine (SSI) equipment [35], which is the most validated system in liver pathology among those that have 2D-SWE. Several advantages can be highlighted: The ROI has the adjustable size, and is larger than the ROI provided by pSWE; the method is ultrasound-guided and has real-time visualization. It is worth mentioning that this technique is feasible in patients with ascites or obesity.

3.4. Strain Elastography (SE)

SE has the lowest applicability for liver evaluation. It involves mechanical stress produced by either palpation with the ultrasound transducer or by physiological movements (heart beats, respiratory movements). The axial displacement is relative to the surrounding tissue and is compared before and after the pressure is applied. With SE, there is substantial variability of the results, due to the inability to quantify the stress and the consequent relative deformability [31,35,60]. This feature is considered a major drawback that limits the use of SE in accurately evaluating diffuse liver diseases. However, SE can be used in the qualitative evaluation of FLL by characterizing the lesion as either soft or hard.

4. Confounders: Factors Influencing Liver Stiffness Independent of Liver Fibrosis

In general terms, the main confounders of elevated liver stiffness are the same for all techniques. They include necroinflammation, congestion, and mechanic cholestasis. Food intake and alcohol consumption can also influence the results. Other diseases that can independently increase the liver stiffness are amyloidosis, lymphomas, and extramedullary hematopoiesis [35,61].

In addition, the software may represent a source of measurement bias. Measured cut-off values are specific for each manufacturer and for each product of the same brand. For this reason, the data provided by different manufacturers should not be pooled together. Therefore, it is recommended to consider the data from a single product to have interobserver comparability [35].

Another disputed error point is whether severe steatosis influences liver stiffness. Petta et al. [62] found that severe steatosis (≥66% at liver biopsy and severe bright liver ultrasound pattern) significantly increases LS values by using the M probe in NAFLD patients. They assumed that the fat droplets in the hepatocytes alter the wave transmission through the liver, increasing the rates of false-positive diagnoses of both significant and severe fibrosis. More recently, similar results for high CAP values by the regular M probe were reported [63]. However, it is debatable whether steatosis directly affects fibrosis measurement. Several studies showed that high BMI and central obesity were independent risk factors for liver stiffness measurement (LSM) unreliability and for a high rate of failure [42,64]. A novel prospective study by Wong et al. [65], found that BMI rather than steatosis was a more important confounder of fibrosis assessment in NAFLD patients. Nevertheless, further studies are required to elucidate this aspect.

5. Indications, Advantages, and Limitations of the Quantitative Ultrasonic Elastography Technology

The main clinical indications for ultrasound elastography in patients with chronic liver diseases are detection, staging, and monitoring liver fibrosis [38]. As exemplified in Table 1, all elastographic

techniques showed promising results in patients with HCV. With a range of 56–100% sensitivity and 32–98% specificity pooled in the European Association for Study of Liver-Asociacion Latinoamericana para el Estudio del Higado (EASL-ALEH) Clinical Practice Guidelines [35], these techniques are being considered as a first-line assessment for liver fibrosis by current protocols [35]. Similarly, in patients with HBV, elastographic methods proved their usefulness in identifying those with cirrhosis with a sensitivity range of 50–100% and a specificity of 38–98%. On the other hand, studies concerning NAFLD subjects are rather scarce, with a large amount of the literature focusing on VCTE, since pSWE and 2D-SWE are newer technologies. Of note is that the control patients in NAFLD studies are individuals with no underlying liver disease. A more comprehensive approach to NAFLD assessment will be presented in the sections below.

Table 1. Summary of advantages and limitations of each quantitative ultrasonic elastography technology. The current clinical indications and the corresponding sensitivity and specificity are described as well, with the mention that studies are underway for several other liver pathologies, including NAFLD.

Elastographic Technique	Indications	Se (Min-Max)/Sp (Min-Max) According to the EASL-ALEH Guide [34]	Advantages	Limitations
VCTE	HCV: First-line assessment [34,35]	56–97%/32–96%	- Less expensive [66], point-of-care examination; - Easy to perform by non-specialized personnel after appropriate training [67]; - Good reproducibility; - The quality criteria are well-defined; - Good diagnostic accuracy for the stages of fibrosis in the liver; - Can assess steatosis using the Controlled attenuation parameter (CAP); - More research work was involved for VCTE in NAFLD patients, compared to the alternatives.	-Low quality in the presence of obesity, congestion, cholestasis, inflammation, and ascites [66,67] (the use of the XL probe reduces the limits in obese patients); -Requires dedicated device; -No image and guidance provided; -Operator and patient-related variability.
	HBV: Useful to identify cirrhotic patients	52–98%/38–98%		
	NAFLD: Can be used to exclude cirrhosis	67–100%/64–91%		
	ALD: Can be used to exclude cirrhosis	80–86%/83–91%		
Point quantification SWE	HCV: First-line assessment [35]	68–100%/70–98%	- Results are less affected by ascites, obesity [68]; - Provides anatomical information; images are provided by B-mode ultrasound conventional system; - Provides the possibility of choosing the ROI; - The accuracy of diagnosis is comparable to VCTE for the stages of fibrosis [69]; - Low operator dependence.	-More expensive; -The quality criteria are not well-defined; -Small ROI size compared to VCTE; -Quality influenced by cholestasis [70]; -Needs experience in B-mode ultrasound; -The method is less evaluated in the literature.
	HBV: Useful to identify cirrhotic patients	50–100%/70–92%		
Two-dimensional SWE (2D-SWE)	HCV: First-line assessment [35]	75.9–91.4%/88.2–90.8% [1]	- Adjustable size of ROI, larger than VCTE and pSWE; - Provides real-time images; - Results are less affected by ascites, obesity [68]; - Provides both anatomical information and tissue stiffness, since B-mode ultrasound images are superimposed to the colored maps of the stiffness; - Low operator dependence; - The range of values is high (5–150 kPa) [69]; - The accuracy of diagnosis is comparable to VCTE for the stages of liver fibrosis [69].	-More expensive; -Needs experienced operator in B-mode ultrasound; -Low quality when depth below 4–5 cm [71]; -Results influenced by food intake [72]; -The method is less evaluated in the literature.
	HBV: Useful to identify those cirrhotic patients	50.7–81.5%/70.4–88.4% [2]		

[1] Se and Sp data available from [73]; [2] Se and Sp data available from [74]. VCTE, vibration controlled transient elastography; pSWE, Point shear wave elastography.

6. Liver Parenchyma Characterization in NAFLD Patients with Superimposed HCC

As NAFLD statistics increase worldwide, it is imperative to identify those with unfavorable prognosis and implement repeatable, non-invasive methods for proper assessment and screening. Elastographic techniques, such as VCTE, pSWE, and 2D-SWE, are recent developments that can accurately evaluate liver stiffness. In general terms, the stiffer the tissue—the greater the amount of liver fibrosis. Concomitantly, liver steatosis can be easily evaluated through VCTE by measuring the aforementioned CAP.

6.1. Performance of VCTE for Liver Fibrosis Assessment in NAFLD

VCTE is a noninvasive, easy-to-perform method that can reliably determine the stage of liver fibrosis in patients with NAFLD by measuring liver stiffness [75–77]. As VCTE presents a high negative predictive value (around 90%), it can be used with great confidence to exclude severe fibrosis and especially cirrhosis, rather than diagnosing these pathological entities [35,78,79].

For several years, numerous studies reviewed the performance of liver stiffness measurement assessed by VCTE, compared to the histological evaluation through liver biopsy, which is considered to be the "gold standard" for fibrosis assessment [35]. As summarized in Table 2, the diagnostic cut-off values for minimal fibrosis (≥F1) using the M probe range from 4.9 to 7 kPa, with 61.7–90% sensitivity and 31–100% specificity. The proposed cut-offs for diagnosing advanced significant fibrosis (≥F2) with the same probe vary between 5.8 to 12.1 kPa, with 40–91.7% sensitivity and 38–94.4% specificity. Moreover, the vast majority of studies that analyzed the cut-off values for detecting severe fibrosis (≥F3) found suggestive LS values of 6.2 to greater than 15 kPa with 28.6–100% sensitivity and 47–98.7% specificity. As expected, the cut-off values for liver cirrhosis are high, varying from 7.9 to 22.3 kPa with 46.9–100% sensitivity and 62–98% specificity, using the M probe. Furthermore, the meta-analysis performed by Xiao et al. [80] recommends 4.8 to 8.2 kPa as the threshold for ruling in stage 2 fibrosis with the new XL probe at an associated 75.8% sensitivity and 64.8% specificity; the same meta-analysis suggests a range between 5.7 to 9.3 kPa for stage 3 fibrosis with 75.3% sensitivity and 74% specificity [80]. The Xiao meta-analysis propounds cut-off values varying between 7.2 to 16 kPa for cirrhosis with 87.8% sensitivity and 82% specificity, when the XL probe is used. Overall, in our reviewed studies, the AUROC ranged from 0.74 to 0.93 for stage 1 fibrosis, 0.757 to 0.987 for stage 2 fibrosis, 0.76 to 0.98 for stage 3 fibrosis, and 0.836 to 0.99 for stage 4 fibrosis.

Table 2. Performance of liver stiffness (LS) cut-off values by VCTE for detecting different stages of liver fibrosis in NAFLD patients.

Fibrosis Stage		≥F1			≥F2			≥F3			≥F4		
Study		Cut-Off (kPa)	AUROC	Se/Sp (%)	Cut-Off (kPa)	AUROC	Se/Sp (%)	Cut-Off (kPa)	AUROC	Se/Sp (%)	Cut-Off (kPa)	AUROC	Se/Sp (%)
Eddowes et al. [81] (*n* = 373)			N/S		8.2 [1] 6.1 [2] 12.1 [3]	0.77	71/70 90/38 44/91	9.7 [1] 7.1 [2] 14.1 [3]	0.80	71/75 90/50 48/90	13.6 [1] 10.9 [2] 20.9 [3]	0.89	85/79 91/70 59/90
Furlan et al. [82] (*n* = 59)			N/S		8.8 [1] 4.8 [2] 8.8 [3]	0.77	51.2/94.4 90.2/50 51.2/94.4	6.7 [1] 6.2 [2] 10.5 [3]	0.86	86.4/70.3 90.9/59.5 50/91.9		N/S	
Hsu et al. [83] (*n* = 230 *)		6.2	0.818	65.6/67.1	7.6	0.866	76.3/79.6	8.8	0.841	77.2/78	11.8	0.836	80/81
Siddiqui et al. [77] (*n* = 393)		4.9	0.74	90/31	8.6 [1] 5.6 [2] 11.9 [3]	0.79	66/80 90/44 40/90	8.6 [1] 6.5 [2] 12.1 [3]	0.83	80.74 90/47 52/90	13.1 [1] 12.1 [2] 14.9 [3]	0.93	89/86 90/82 69/90
Wong et al. [65] (*n* = 496)	M probe		N/S			N/S		> 15 kPa	0.90	28.6/98.7	>15 kPa	0.87	46.9/95.5
	XL probe		N/S			N/S			0.80	31.3/96.5		0.86	48.6/93
Jiang et al. [84] (*n* = 1753 *)			N/S		N/S	0.85	77/80	N/S	0.92	79/89	N/S	0.96	90/91
Lee et al. [85] (*n* = 94)			N/S		7.4	0.757	62.5/91.7	8.0	0.870	82.6/84.9	10.8	0.882	91.7/81.2
Petta et al. [63] (*n* = 324)			N/S		8.5	0.808	N/S	10.1	0.861			N/S	
Xiao et al. [80] (*n* = 429 *)	M probe		N/S		5.8 6.65–7 7.25–11	0.83	91.7/57.4 74.1/68.8 65.7/84.5	6.95–7.25 7.6–8 8.7–9 9.6–11.4	0.87	69.2/66.3 88.9/77.2 83.3/78 80.1/89.9	7.9–8.4 10.3–11.3 11.5–11.95 13.4–22.3	0.92	96.5/77.7 87.7/86.3 77.5/88.8 78.2/90.8
	XL probe		N/S		4.8–8.2	0.82	75.8/64.8	5.7–9.3	0.86	75.3/74	7.2–16	0.94	87.8/82
Boursier et al. [86] (*n* = 452)			N/S		N/S	0.842	N/S	8.7	0.831	88.4/62.9	N/S	0.864	N/S
Cassinotto et al. [87] (*n* = 291)			N/S		6.2	0.82	90/45	8.2	0.86	90/61	9.5	0.87	92/62
Imajo et al. [88] (*n* = 142)		7	0.78	61.7/100	11	0.82	65.2/88.7	11.4	0.88	85.7/83.8	14	0.92	100/75.9
Pathik et al. [89] (*n* = 110)			N/S		9.1	N/S	N/S	12	0.91	90/80	20	N/S	90/80
Kwok et al. [90] (*n* = 854)			N/S		6.7–7.7	0.79–0.987	79/75	8–10.4	0.76–0.98	85/85	10.3–17.5	0.91–0.99	92/92
Kumar et al. [78] (*n* = 205)		6.1	0.82	78/68	7	0.85	77/78	9 [5] 7.8 [2] 11.2 [3]	0.94	85/88 96/78 71/93	11.8 [5] 10.6 [2] 19.4 [3]	0.96	90/88 100/82 70/98
Myers et al. [43] (*n* = 75)	M probe		N/S		7.8	0.86	82/78	N/S	0.87	N/S	22.3	0.88	80/91
	XL probe		N/S		6.4	0.85	81/66	N/S	0.90	N/S	16.0	0.95	100/91
Lupsor et al. [91] (*n* = 72)		5.3	0.879	86.1/88.9	6.8	0.789	66.67/84.31	10.2	0.978	100/96.87		N/S	
Wong et al. [92] (*n* = 246)			N/S		5.8 [2] 7 [4] 9 [3]	0.84	91.1/50.3 79.2/75.9 52.5/91.7	7.9 [2] 8.7 [4] 9 [3]	0.94	91.1/75.3 83.9/83.2 75/91.6	10.3 [2] 10.3 [4] 11.4 [3]	0.95	92/87.8 92/87.8 76/91
Yoneda et al. [76] (*n* = 97)		5.9	0.93	86.1/88.9	6.65	0.865	88.2/73.9	9.8	0.904	85.2/81.4	17.5	0.991	100/96.6

* meta-analysis, N/S = not specified. [1] Youden's Index, YI; [2] Se > 90%; [3] Sp > 90%; [4] max diagnostic accuracy, DA ; [5] Se + Sp max.

VCTE—Impediments and Resolutions

The main challenge with the VCTE technique is to obtain valid acquisitions in high BMI patients, as abdominal obesity hampers the transmission of the shear wave [35,93]. Different studies have reported unreliable results (11.6–15.8%) and a high rate of failure (2.7–23%), mostly because of increased BMI (≥28 kg/m^2) along with elevated waist circumference [42,43,76,79,91,92,94,95]. Other features of the metabolic syndrome, together with limited operator experience, correlate with measurement failure [94]. These findings strengthen the need to validate the new XL probe, designed for obese patients, that should be used when the skin-to-liver capsule distance (SCD) is greater than 25 mm [34]. Multiple studies reported that when used in the same patient, the XL probe generates lower measurement than the M probe. Therefore, it has been thought that the cut-off values for the XL probe should be lower, around 1.5–2 kPa, than the ones used for the standard M probe [35,40,68,96,97]. However, in a novel prospective study [65], Wong et al. found that the same LS cut-off values can be used for both M and XL probe in clinical practice, when used in patients with BMI <30 kg/m^2 and ≥30 kg/m^2, respectively, as the high BMI independently increases liver stiffness values [98].

6.2. pSWE Performance in Assessing Fibrosis in NAFLD

We identified several studies that assessed point shear wave elastography-ARFI in NAFLD patients [87,99–103]. A systematic review and meta-analysis by Liu et al. [104] found that ARFI elastography has modest accuracy (about 90%) in detecting significant fibrosis in NAFLD patients, with 80.2% sensitivity and 85.2% specificity. These values are considered an inappropriate endpoint by the ESFUMB guidelines [35]. However, Friederich-Rust et al. [68] found that ARFI has similar diagnostic accuracy to VCTE in detecting significant and severe fibrosis, in line with the results of the meta-analysis conducted by Jiang et al. [84]. In a novel 2020 systematic review and meta-analysis by Lin et al. [105], which included 1147 NAFLD patients, the AUROC was 0.89, 0.94, and 0.94 for the diagnosis of stages 2, 3, and 4 of fibrosis, respectively. Considering these contradictory results, further longitudinal studies should clarify its performance for monitoring patients with NAFLD. Overall, the AUROC systematized in Table 3 ranges from 0.657 to 0.944 for advanced fibrosis, 0.71 to 0.982 for severe fibrosis, and 0.74 to 0.984 for cirrhosis prediction.

Compared to other elastographic techniques, several studies investigated the ability of ARFI to distinguish between patients with NASH from those with simple steatosis, concluding that pSWE is a promising tool with AUROC varying from 0.867 to 0.899 [101,102].

6.3. Performance of 2D-SWE in Evaluating Fibrosis in NAFLD Patients

2D-Shear Wave Elastography is a relatively new FDA-approved technique that measures liver stiffness using acoustic radiation force and ultrafast ultrasound imaging [87], with limited research on the diagnostic accuracy in NAFLD. Two meta-analyses [106,107] that included 2303 and 934 patients with chronic liver diseases, respectively, evaluated the performance of 2D-SWE in assessing liver fibrosis. The pooled sensitivity and specificity of SWE were 76% and 92% for ≥ F1, with an AUROC of 0.85. The summary AUROC was 0.87–0.88 for ≥ F2 with a sensitivity of 84–85% and a specificity of 81–83%. For ≥ F3 the pooled sensitivity and specificity were 89–90% and 81–86%, respectively, corresponding to an AUROC of 0.93–0.94. The pooled sensitivity and specificity for ≥ F4 were 87–88% and 88–89%, with AUROC 0.92–0.94.

Furthermore, recent studies on NAFLD patients suggest that this elastographic method achieved good diagnostic performance, with AUROC values ranging from 0.75 to 0.89 for ≥ F2, 0.8 to 0.95 ≥ F3, and 0.88 to 0.97 for F4, being particularly useful in detecting lower stages of fibrosis with AUROC values of 0.82 for ≥ F1 [108,109], as exemplified in Table 4. Regarding the cut-off values for different fibrosis stages, Cassinotto et al. [87] showed that most of them are very close to the corresponding VCTE values for ruling out the pathologies

Table 3. Performance of ARFI for detecting different stages of liver fibrosis in NAFLD patients.

Fibrosis Stage	≥F2			≥F3			≥F4		
Study	**Cut-Off (m/s)**	**AUROC**	**Se/Sp (%)**	**Cut-Off (m/s)**	**AUROC**	**Se/Sp (%)**	**Cut-Off (m/s)**	**AUROC**	**Se/Sp (%)**
Lin et al. (*n* = 1147 [1]) [105]	1.3	0.89	85/83	2.06	0.94	90/90	1.89	0.94	90/95
Jiang et al. (*n* = 982 [1]) [84]	N/S	0.86	70/84	N/S	0.94	89/88	N/S	0.95	89/91
Lee et al. (*n* = 94) [85]	1.35	0.657	46.2/93.2	1.43	0.873	70/93.7	1.50	0.92	75/90.7
Cassinotto et al. (*n* = 291) [87]	0.95 1.32	0.77	90/36 56/91	1.15 1.53	0.84	90/63 59/90	1.3 2.04	0.84	90/67 44/90
Cui et al.(*n* = 125) [110]	1.34	0.848	81.8/78.3	1.34	0.896	95.2/74	2.48	0.862	77.8/93.1
Fierbinteanu et al. (*n* = 64) [101]	1.165	0.944	84.8/90.3	1.48	0.982	86.4/95.2	1.635	0.984	91.7/92.3
Cassinotto et al. (*n* = 321) [111]	1.38	0.81	71/78	1.57	0.85	75/80	1.61	0.88	74/78
Friedrich-Rust et al. [2] (*n* = 57) [68]	N/S	0.66	N/S	N/S	0.71	N/S	N/S	0.74	N/S
Osaki et al. (*n* = 23 [3]) [103]	1.79 ± 0.78	N/S	N/S	2.20 ± 0.74	N/S	N/S	2.90 ± 1.01	N/S	N/S
Yoneda et al. (*n* = 54) [112]		N/S		1.77	0.93	100/91	1.90	0.937	100/96

[1] meta-analysis, [2] ARFI measurement for the right lobe, [3] NASH patients.

Table 4. Performance of LSM was assessed by 2D-SWE for detecting different stages of liver fibrosis in patients with NAFLD.

Fibrosis Stage	≥F1			≥F2			≥F3			≥F4		
Study	**Cut-Off (kPa)**	**AUROC**	**Se/Sp (%)**	**Cut-Off (kPa)**	**AUROC**	**Se/Sp (%)**	**Cut-Off (kPa)**	**AUROC**	**Se/Sp (%)**	**Cut-Off (kPa)**	**AUROC**	**Se/Sp (%)**
Lee et al. (*n* = 102) [108]	6.3	0.82	63/88	7.6	0.87	89/77	9.0	0.95	100/85		N/S	
Herrmann et al. (*n* = 156) [113]		N/S		7.1	0.855	N/S	9.2	0.928	N/S	13.0	0.917	N/S
Takeuchi et al. (*n* = 71) [109]	6.61	0.82	79/67	11.57	0.75	52/44	13.07	0.82	63/57	15.73	0.90	100/82
Lee et al. (*n* = 94) [85]		N/S		8.3	0.759	87/55.3	10.7	0.809	90/61.2	15.1	0.906	90/78
Xiao et al. (*n* = 429 [1]) [80]		N/S		2.67–9.4	0.89	85/94.4	3.02–10.6	0.91	89.9/91.8	3.36	0.97	100/85.6
Cassinotto et al. (*n* = 291) [87]		N/S		6.3 [3] 8.7 [4]	0.86	90/50 [3] 71/90 [4]	8.3 [3] 10.7 [4]	0.89	91/71 [3] 71/90 [4]	10.5 [3] 14.5 [4]	0.88	90/72 [3] 58/90 [4]
Ochi et al. (*n* = 181) [114]	2.47 [2]	0.838	0.649/0.969	2.76 [2]	0.853	86/88.6	3.02 [2]	0.878	88.2/91.5	3.36 [2]	0.965	100/85.6

[1] meta-analysis, [2] study used elastic ratio, [3] for Se ≥ 90%, [4] for Sp ≥ 90%.

6.4. Steatosis Evaluation in NAFLD Patients Using the Controlled Attenuation Parameter (CAP)

VCTE is able to measure the LS and CAP simultaneously [40]. The latter evaluates the amount of liver steatosis, defined as fat accumulation in the hepatocytes, the only histopathological factor that influences this parameter [115–117]. In comparison, the conventional B-mode US provides a subjective estimation of fatty infiltration and is mostly unreliable in detecting mild steatosis [118].

A 2016 meta-analysis involving 2735 patients (with a 20% intra-study prevalence of NAFLD) provided the optimal CAP cut-off values of 248 dB/m, 268 dB/m, and 280 dB/m for the prediction of mild, moderate, and severe steatosis, respectively. According to this meta-analysis, covariates, such as etiology, BMI, and diabetes, should be taken into consideration when interpreting CAP, although sex, age, and fibrosis have been shown to play a rather minor role. The authors recommend using the aforementioned cut-off values, but deducting 10 dB/m from the CAP value for NAFLD/NASH patients, 10 dB/m for diabetes patients, and deducting/adding 4.4 dB/m for each unit of BMI above or below 25 kg/m^2 and over the range of 20–30 kg/m^2 [49].

Furthermore, in a recent meta-analysis by Pu et al. involving 1297 biopsy-proven NAFLD patients, the mean AUROC value of CAP was 0.96, 0.82, and 0.70 for diagnosing mild, moderate, and severe steatosis, respectively [119]; the Pu study did not provide any cut-off values for NAFLD patients.

6.5. Prognosis Value of LS and CAP Measurement in NAFLD

It is imperative to assess the fibrosis stage in NAFLD patients, as it represents the key prognostic factor for liver-related events [120–122]. Mortality rises by a factor of 50–80 for NAFLD patients with severe fibrosis (F3) or cirrhosis (F4) compared to those with mild or no fibrosis [13]. In a retrospective cohort study on 646 biopsy-proven NAFLD patients, Hagström et al. [123] found that NASH did not affect the outcomes of patients in a significant manner, whereas, higher stages of fibrosis did.

In a recent prospective study on 2551 NAFLD patients, Shili-Masmoudi et al. [124] demonstrated that LS is an independent predicting factor for overall survival, liver-related and cardiovascular events, supporting the meta-analysis findings of Singh et al. [125]. Shili-Masmoudi also showed that the HCC incidence rises with baseline LS from 0.32% (if LS < 12 kPa) to 0.58% (if LS ranges between 12–18 kPa), 9.26% (if LS ranges between 18–38 kPa) and 13.3% (if LS >38 kPa) [124]. Moreover, several studies established the association between LS and the risk of HCC development in patients with chronic hepatitis C [126–128] and chronic hepatitis B [129,130], providing effective risk prediction models [131–133]. However, existing literature does not offer any model for NAFLD-related HCC risk.

Boursier et al. [86] evaluated the prognostic significance of LS in NAFLD, recommending a new clinically relevant fibrosis classification using seven classes of fibrosis: LSM1 (between 2.0 and 4.6 kPa), LSM2 (4.6 to 6.1 kPa), LSM3 (6.1 to 8.8 kPa), LSM4 (8.8 to 12.0 kPa), LSM5 (12.0 to 18.0 kPa), LSM6 (with a large interval between 18.0 to 38.6 kPa) and LSM7 (when liver stiffness is greater than 75.0 kPa). In the Boursier study, overall survival progressively decreased with increasing LS. For instance, overall survival for LSM1 in ten years was close to 1.0, indicating almost perfect concordance; whereas, for LSM7, the Harrel-C index was near 0.3 [86].

Regarding the prognostic value of CAP, studies are rather scarce and have conflicting results. Margini et al. reported that a CAP > 220 dB/m was independently associated with a higher risk of relevant clinical events [134]. On the other hand, Liu et al. reported that neither the presence nor the severity of liver steatosis as measured by CAP forecasted cancer, liver-related or cardiovascular events [135]. These results are in line with the latest results of Scheiner and colleagues [136]. Therefore, further research is necessary to elucidate the prognostic role of CAP among NAFLD patients.

7. Ultrasound Elastography: A New Tool in the Characterization of Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease

As exemplified so far, elastography is a powerful non-invasive diagnostic tool used in a number of diffuse liver diseases, including NAFLD. In addition, ultrasound elastography is able to characterize focal liver lesions (FLLs), providing supplementary information to the diagnostician.

In the context of NAFLD, elastography may play an important role in differentiating HCC, a known complication of this disease, from other focal liver lesions. Of note is the high incidence of HCC that arises from a NAFLD-affected liver in the absence of fibrosis or cirrhosis [9]. Indeed, it is abundantly clear that an in-depth stiffness measurement of the FLL should invariably be associated with the elastographic evaluation of the background liver. It is worth mentioning that there is a large FLL stiffness value overlap between benign and malignant FLL, which limits the accurate use of elastography for the diagnosis of a specific FLL in this type of patient.

From a technical perspective, VCTE is not able to characterize the stiffness of a single FLL. Of note are several studies that investigated the role of VCTE for HCC prediction in cirrhotic patients of specific viral etiology, or to correlate liver stiffness measurements with survival and prognosis; these studies identified a statistically significant correlation between a higher liver stiffness baseline value and the risk of developing HCC in patients with B and C chronic viral hepatitis [125,129,137,138]. We found no studies that focused on the diagnostic capability of VCTE in NAFLD-related HCC.

7.1. The Evaluation of FLLs Using pSWE Methods

Considering that pSWE is a noninvasive and reproducible method that can be used in liver fibrosis assessment, several recent studies sought to investigate pSWE performance for FLL evaluation, with a target to differentiate the large number of FLLs and to characterize their cancerous/benign state [139–154].

ARFI measures of FLLs are best interpreted in the context of the liver background, as it may suggest an FLL on diffuse liver disease. We reiterate the idea that HCC can arise on several altered liver backgrounds, such as cirrhotic livers of different etiologies and even NAFLD-affected livers. Table 5 presents a collection of shear wave velocity values (mean in m/s, range) measured by pSWE in different types of FLLs: HCC, metastases, hemangiomas, focal nodular hyperplasia (FNH), and adenomas, as well as the corresponding SWV cut-off values (m/s) for discriminating between the malignant versus benign FLL status. Literature data suggest that malignant FLLs are generally stiffer than their benign counterparts [152,155]; HCCs are overall softer than other malignant tumors [140,141,143], with SWS values varying from 2.17 ± 0.85 m/s in the Gallotti study [143] to 3.07 ± 0.89 m/s in the Guo study [146]. Several elastographic FLL studies report the following descending order of stiffness, based on the ARFI method: Metastases > HCC > FNH > hemangiomas [140,147,148]. Of note is the SWV value similarity between different pathological processes, such as between HCC and FNH [147,148] and even between the malignant category and the benign category in the Dong study [145]. A plausible explanation for these overlaps include the level of fibrous tissue in the focal lesion, as well as the vascularization; whilst fibrous tissue tends to increase stiffness, highly vascularized lesions tend to be softer [152]. These factors may limit the diagnostic capability of ARFI for the precise diagnostic of the FLL. Nevertheless, several studies concluded that pSWE presents promising utility in discriminating between HCC versus other FLLs [156].

Table 5. A collection of shear wave velocity values (mean in m/s, range) for a predefined number of focal liver lesions (FLLs) in different studies, using the pSWE technology. The table includes the SWV cut-off values (m/s) for discriminating malignant versus benign FLLs, their corresponding sensitivity (Se) and specificity (Sp), as well as the statistical interpretation of the discrimination of HCC lesions from others.

Study	Cut-Off Value Malignant Versus Benign (m/s)	Se/Sp (%)	HCC	Metastases	Hemangiomas	FNH	Hepatocellular Adenoma	Statistically Significant/Not Significant Difference between SWV of HCC and Other FLLs
Park et al. [139]	1.82	71.8/75	2.48 ± 0.84 (n = 24)	2.35 ± 1.18 (n = 8)	1.83 ± 0.62 (n = 5)	0.97 ± 0.48 (n = 3)	N/S	Significant difference: HCC—benign lesions (p = 0.006)
Akdogan et al. [140]	2.32	93/60	2.75 ± 0.53 (n = 10)	3.59 ± 0.51 (n = 22)	2.15 ± 0.73 (n = 34)	3.22 ± 0.18 (n = 4)	N/S	No significant difference: HCC—hemangiomas (p > 0.05) Significant difference: HCC—metastatic lesions (p < 0.05)
Kim et al. [141]	2.73	96.4/65.8	2.66 ± 0.94 (n = 26)	2.82 ± 0.96 (n = 24) with colon cancer metastasis 3.70 ± 0.61 (n = 20)	1.80 ± 0.57 (n = 28)	N/S	N/S	No significant difference: HCC—hemangiomas (p > 0.05)
Davies et al. [142]	2.5	97.1/100	N/S	4.23 ± 0.59 (n = 10)	1.35 ± 0.48 (n = 35)	N/S	N/S	N/S
Gallotti et al. [143]	N/S	N/S	2.17 ± 0.85 (n = 6)	2.87 ± 1.13 (n = 9)	2.30 ± 0.95 (n = 7)	2.75 ± 0.95 (n = 13)	1.25 ± 0.37 (n = 5)	No significant difference: HCC—hemangiomas. Significant difference: HCC—adenomas (p < 0.05)
Frulio et al. [144]	N/S	N/S	2.4 ± 1.01 (n = 24)	3.0 ± 1.36 (n = 12)	2.14 ± 0.49 (n = 15)	3.14 ± 0.63 (n = 19)	1.90 ± 0.86 (n = 9)	No significant difference: malignant—benign groups (p N/S).
Dong et al. [145]	2.06	80.6/88	2.63 (range 1.84–5.68) (n = 104)	2.78 (range 1.02–3.15) (n = 11)	1.5 (range 0.79–2.61) (n = 11)	1.35 (range 0.69–2.94) (n = 5)	N/S	Significant difference: Malignant—benign lesions (p < 0.05)
Guo et al. [146]	2.13	83.3/77.9	3.07 ± 0.89 (n = 24)	2.74 ± 1.06 (n = 26)	1.48 ± 0.70 (n = 47)	2.30 ± 1.18 (n = 7)	N/S	Significant difference: HCC—hemangiomas (p < 0.001) Significant difference: HCC—focal fatty degeneration (not mentioned in the current table, p = 0.006)
Zhang et al. [147]	2.16	81.3/74.1	2.59 ± 0.91 (n = 61)	3.20 ± 0.62 (n = 39)	1.33 ± 0.38 (n = 28)	1.90 ± 0.45 (n = 14)	N/S	Significant difference: Malignant—benign lesions (p < 0.01)
Yu et al. [148]	2.72	69/89	2.49 ± 1.07 (n = 28)	2.73 ± 0.89 (n = 13)	1.75 ± 0.80 (n = 35)	2.18 ± 0.84 (n = 15)	1.79 ± 0.14 (n = 2)	Significant difference: HCC—benign lesions (p < 0.01, overlap) Significant difference: HCC—hemangiomas (p < 0.01)

Heide et al. [149]	N/S	N/S	2.63 ± 1.09 (*n* = 5)	2.88 ± 1.16 (*n* = 17)	2.36 ± 0.77 (*n* = 13)	3.11 ± 0.93 (*n* = 17)	2.23 ± 0.97 (*n* = 2)	No significant difference: Malignant—benign lesions ($p = 0.23$).
Galati et al. [150]	2.0	74.6/80.7	2.47 ± 1.425 (*n* = 39)	3.29 ± 1.2325 (*n* = 28)	1.34 ± 0.9125 (*n* = 52)	N/S	N/S	Significant difference: Malignant lesions—hemangiomas (*p* N/S)
Cho et al. [151]	2.0	74/82	2.45 ± 0.81 (*n* = 17)	2.18 ± 0.96 (*n* = 8)	1.51 ± 0.71 (*n* = 17)	N/S	N/S	Significant difference: HCC—hemangiomas ($p < 0.05$)
Wu et al. [152]	2.22	51.9/85.7	Malignant: 2.25 ± 0.80 (*n* = 27)		Benign: 1.70 ± 0.58 (*n* = 28)			Significant difference: Malignant—benign lesions ($p = 0.007$)
Shuang-Ming et al. [153]	2.22	89.7/95	Malignant: 3.16 ± 0.80 (*n* = 68)		Benign: 1.47 ± 0.53 (*n* = 60)			Significant difference: Malignant—benign lesions ($p < 0.001$)
Kapoor et al. [154]	2.5	88/83	2.4 (range 1.28–3.5) (*n* = 7)	3.28 (range 2.9–3.65) (*n* = 18)	Benign: 1.83 (range 1.26–2.39) (*n* = 15)			Significant difference: HCC—metastatic nodules ($p = 0.008$)

pSWE evaluation of FLLs has several limitations and error points that are worth discussing. First and foremost, the maximum depth of pSWE examination is limited to 8 cm from the skin, due to safety concerns [157,158]; therefore, lesions situated below 8 cm cannot be examined. Another pSWE limitation relates to the susceptibility of motion-related factors that can lead to an inaccurate reading of the SWV; the inaccuracy increased when the focal lesion was located close to the heart or large blood vessels, as well as in patients unable to keep the breath-hold [159]. Furthermore, the wide range of stiffness values/SWVs of FLLs leads to value overlapping between malignant and benign lesions, leading to a diagnostic confusion [144]. Sampling bias is another error point that is worth mentioning [152]; Frulio et al. suggested that different measurement findings in studies that compare benign versus malignant lesions can be explained by different proportions of these FLLs in the study samples. For example, a significantly larger number of patients with FNH could increase the mean SWV value of the benign FLLs group, as was the case in the same study by Frulio et al. [144]. Last, but not least, we mention the limitations that may arise regarding the study design (inclusion/exclusion criteria) and the operator's experience. Nevertheless, ARFI still remains a powerful and essential diagnostic tool in the differential evaluation of FLLs.

7.2. 2D-SWE Evaluation of FLLs

2D-SWE has been used in multiple clinical instances, such as discriminating with high specificity between malignant and benign lesions in the prostate [160], thyroid [161], breast [162], and more recently, for the non-invasive characterization of focal liver lesions [163,164]. Compared to pSWE, 2D-SWE supersonic shear imaging allows the display of color maps with quantitative data [165], further enlarging the information palette that elastography could potentially bring in the diagnosis of HCC in NAFLD. There are studies that evaluated the stiffness of FLLs using 2D-SWE [164,166–170]. HCC presents a large palette of stiffness values in 2D-SWE imaging, varying from 19.6 kPa in the 1 case included by Ronot et al. [164] to 44.8 kPa (range 15.8 kPa-97 kPa) in the Gerber study [170]. This variability can be explained by a multitude of factors, including lesion dimensions and the ROI positioning (peripheral—stiffer versus central—softer).

Furthermore, as objectified by Hwang et al. [171], the background liver plays an important role in the FLL diagnostic capability of 2D-SWE. In NAFLD patients, the liver can be fibrotic, which further hampers the stiffness measurement of FLLs, making it difficult to evaluate a malignant lesion versus a benign lesion. In the same phantom study by Hwang et al., the inclusion's (FLL mimic) stiffness was increased when the inclusion was engulfed in a stiffer background, e.g., an FLL on a fibrotic liver [171]. A study by Grgurevic et al. concluded that a comprehensive 2D-SWE approach—defined as the statistical analysis of FLL stiffness, FLL to non-infiltrated liver stiffness ratio, as well as the intralesional variation of stiffness—would be able to differentiate between malignant FLLs and benign FLLs in 96% of patients [169]. In general terms, benign FLLs present as softer than their malignant counterparts [167,170].

Moreover, a recent study by Wang et al. [168] used an ultrasomics technique to investigate the possibility of discriminating malignant FLLs from benign FLLs through 2D-SWE. The team calculated an ultrasomics score (generated by a support vector machine from 15 ultrasomics features that were statistically obtained by Spearman correlation), as well as a combined score (generated by analyzing 4 SWE measurements and 15 ultrasomics features), to identify the method with the highest statistical accuracy. The authors focused their FLL study on two separate ROI point measurements (one peripheral and one central), to increase the measurement accuracy, as the literature reports different stiffness values in different points of the same FLL. Both the ultrasomics score and the combined score presented advantages compared to conventional 2D-SWE in differentiating malignant FLLs from benign FLLs with 0.96 AUC for both scores in the training cohort, as well as 0.91 AUC and 0.94 AUC, respectively, in the validation cohort. Furthermore, the combined score showed better diagnostic performance compared to the ultrasomics score and SWE measurements alone, suggesting a great potential of the ultrasomics method in discriminating between malignant FLLs and benign FLLs [168]. Table 6 presents the mean FLL stiffness values measured by 2D-SWE with the associated cut-off values for differentiating malignant FLLs from benign FLLs.

Table 6. Mean stiffness values (kPa) of FLLs measured by 2D-SWE with the associated cut-off values to differentiate malignant FLLs from benign FLLs.

Study	Cut-Off Value Malignant Versus Benign	Se/Sp (%)	HCC	Metastases	Hemangiomas	FNH	Hepatocellular Adenoma	Statistically Significant/Not Significant Difference between Stiffness of HCC and Other FLLs
Tian et al.[1] [166]	39.60	87.74/83.67	61.83 ± 28.87 (n = 103)/Parenchyma: 15.94 ± 7.37	90.32 ± 54.71 (n = 35)/Parenchyma: 10.93 ± 36.64	20.56 ± 10.74 (n = 37)/Parenchyma: 9.04 ± 2.44	38.72 ± 18.65(n = 15)/Parenchyma: 9.09 ± 2.64	N/S	Significant difference: Intrahepatic cholangiocarcinomas—HCC (p < 0.0001) Significant difference: metastases—HCC (p = 0.0237) Significant difference: malignant—benign lesions (p < 0.001) Significant difference: HCC—FNHs (HCC > FNH, p = 0.0012)
Guibal et al. [167]	N/S	N/S	14.86 ± 10 (n = 26)	28.8 ± 16 (n = 53)	13.8 ± 5.5 (n = 22)	33 ± 14.7 (n = 16)	9.4 ± 4.3 (n = 10)	Significant difference: HCC—cholangiocarcinomas (p = 0.0004) Significant difference: HCC—metastases (p = 0.0059)
Wang et al. [168]	25.76 (Emean), 0.85 (combined score)	92.59/87.50 (combined score)	39.31 ± 12.50 (n = 83)	56.99 ± 33.13 (n = 24)	13.71 ± 9.24 (n = 33)	30.56 ± 11.86 (n = 11)	N/S	N/S
Ronot et al. [164]	N/S	N/S	19.6 (n = 1)	N/S	17.1 ± 7 (n = 20)	33.3 ± 12.7 (n = 60)	19.7 ± 9.8 (n = 17)	No significant difference: Malignant—benign lesions (p = 0.64)
Grgurevic et al. [169]	22.3	83/86	29.57 ± 11.67 (n = 57)	37.93 ± 10.61 (n = 94)	14.10 ± 6.44 (n = 71)	30.51 ± 32.05 (n = 20)	N/S	Significant difference: Malignant—benign lesions (p < 0.001)
Gerber et al. [170]	20.7	79.7/62	44.8 (range 15.8–97) (n = 16)	29.5 (range 4.1–142.9) (n = 41)	16.35 (range 5.4–71.9) (n = 18)	16.55 (range 2.1–69.7) (n = 18)	8.9 (n = 1)	Significant difference: Malignant—benign lesions (p < 0.0001) Significant difference: Cholangiocarcinomas—HCC (p = 0.033) Significant difference: Cholangiocarcinomas—metastases (p = 0.0079)

[1] only maximal stiffness values presented within the paper.

Two 2D-SWE studies by Guibal et al. [167] and Ronot et al. [164] found no significant differences between malignant and benign FLL stiffness. However, these studies had considerable limits. Guibal et al. suggested that a single diagnostic threshold would not present clinical value to discriminate between malignant and benign FLLs [167]. Ronot et al. included only a small percentage of patients with malignant lesions, which can cause a statistical bias in sampling [164]. There are several other limitations that must be mentioned. First and foremost, this technique cannot evaluate lesions situated over the general SWE limit—8 cm from the skin. Another patient-related limitation is connected to poor image acquisition, due to poor intercostal window and patient's inability to hold the respiration when prompted [168]. Last, but not least, we mention the limitations that may appear in regard to the study design (inclusion/exclusion criteria), the heterogeneity of the lesions (e.g., the heterogeneity of different types of metastases), the operator's experience with 2D-SWE, and the value overlaps. Although the reviewed papers present a great potential of 2D-SWE in characterizing malignant lesions, including HCC on a NAFLD-affected liver, further studies are required to evaluate the accuracy of this method and set specific cut-off values.

8. Conclusions

The rapidly growing prevalence of NAFLD and the implied higher risk of HCC development prompt for new diagnostic tools for both NAFLD and the NAFLD-related HCC. By non-invasive, disease-specific surveillance tools, such as US elastography, a subset of the non-cirrhotic NAFLD patients with a risk for developing HCC can be detected early, leading to a better outcome.

As a rather new and rapidly expanding field in hepatology, US elastography possesses many advantages in characterizing both diffuse and focal liver pathologies. This ultrasound-based method adds a new dimension to the characterization of the background liver and the FLL. Moreover, US elastography provides a rapid, non-invasive and inexpensive method for the clinician to evaluate liver steatosis (using CAP measurement) and fibrosis (using liver stiffness measurement), thus adding a new dimension to the conventional US examination of the background liver. Possessing both diagnostic and prognostic capabilities, US elastography contributes to better surveillance of the underlying liver disease. Furthermore, the development of new elastographic techniques, such as pSWE and 2D-SWE, opened the possibility of evaluating FLLs' stiffness, providing a new category of data that may help in distinguishing between malignant and benign lesions. A comprehensive 2D-SWE approach has been reported to be able to differentiate malignant FLLs from benign FLLs in 96% of cases. In general terms, multiple studies reported a pattern related to FLL stiffness—metastases > HCC > FNH > hemangiomas—that may guide the physician towards the next step of the clinical reasoning. However, the present state of the literature emphasizes the imperfection of this method as a diagnostic tool, as there are no standardized cut-off values for differentiating between malignant and benign liver lesions.

Current US elastography techniques present a number of drawbacks, including a maximum evaluation depth of 8 cm, sensitivity to motion factors, and in some cases, overlapping stiffness values between malignant and benign FLLs. Nevertheless, despite the existing drawbacks, our opinion is that US elastography brought a new and innovative method to characterize FLLs. While we objectified its potential, we find that further studies are required to investigate the accurate characterization of HCC in NAFLD patients, considering the existing technical and conceptual limitations of these elastographic methods. We propose that further studies should focus on the interrelation of the HCC lesion with the background liver and thoroughly characterize the potential intralesional heterogeneity of the HCC lesion, for a comprehensive view upon the existing pathology.

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ORIGINAL RESEARCH

Lifestyle and Cancer Prevention—Opinions and Behaviors Among Romanian University Students

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Background: Healthy lifestyle promotion represents an important component of cancer prevention. The aim of this study is the assessment of opinions and behavior related to healthy lifestyle and cancer prevention among Romanian university students.

Methods: A cross-sectional study was performed by anonymous questionnaires in 2017 among 400 university students from the four main universities from Cluj-Napoca, Romania.

Results: One out of five students was overweight or obese, but 83% meet the recommendations for performing physical activity. The majority did not meet the recommendations of eating 400 g of fruits and vegetables daily, while almost half declared eating more than 500 g of red meat weekly and more than one third do not respect the recommendations for alcohol consumption. The factor analysis reveals two factors with regard to cancer prevention-related behaviors. The first one consists of those having an appropriate body weight, and having a higher tendency for consumption of fruits and vegetables, performing physical activity, while being more prone not to respect the recommendations regarding the alcohol consumption. The second factor refers to a higher tendency to respect both the recommendations for alcohol and red meat consumption.

Conclusion: Future educational activities should focus on promoting better nutritional habits, decrease alcohol consumption and offer appropriate services for weight management among Romanian university students.

Keywords: nutrition, physical activity, students, cancer prevention

Introduction

Healthy lifestyle promotion represents an important component of cancer prevention.[1,2] The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published Diet, Nutrition, Physical Activity, and Cancer: A Global Perspective, the WCRF/AICR second expert report in 2007 and it was revised and updated as the third report published in 2018.[3,4] The reports contain recommendations and, as underlined by an expert panel that authored these recommendations, each of them was intended as one part of a comprehensive package of modifiable lifestyle behaviors which together, promote a healthy pattern of diet and physical activity which help the prevention of cancer, but also non-communicable diseases, and obesity.[4,5]

Recently the 2018 WCRF/AICR Score, (a practical tool that operationalizes eight of the ten 2018 WCRF/AICR cancer prevention recommendations), proposed maintaining a healthy body weight, adoption of an active lifestyle, consumption of a diet rich in whole grains, vegetables, fruit and beans, limit consumption of "fast foods" and other processed foods high in fat, starches or sugars, limit consumption

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of red and processed meat, limit consumption of sugar-sweetened drinks, limit alcohol consumption, and (optional for mothers) breastfeed your baby, if you can. The tool is structured in such way that higher score reflects greater adherence to the recommendations.[5] It is emphasized that the implementation of this standardized score in epidemiologic and clinical studies will enhance comparability of findings across populations and countries.[5]

In recent years several studies investigated the knowledge, attitudes and practices with regard to cancer prevention recommendations among adults from different countries, including one study which investigated these issues among Romanian adults having relatives with cancer.[6–12] There are also recent studies which used the 2018 WCRF/AICR Score.[13–15]

Several studies investigated knowledge, attitudes and behaviors related to dietary habits, physical activity and cancer prevention among the younger population such as university students, but to the best of our knowledge no study used the 2018 WCRF/AICR Score, which focuses on promoting a healthy diet across the lifespan, favorable to the prevention of different types of cancer as well as other chronic diseases.[16–21] University students transit a life period when they become more independent, have a busy schedule, maybe even live apart from their parents, and hence being responsible for choosing, buying and cooking their food, deciding the content, the quantity and the time of their meals and snacks as well as other lifestyle behaviors such as physical activity and alcohol consumption.[22,23] The habits formed during youth with regard to composition and quality of the diet, involvement in physical activity and alcohol consumption are influenced by several individual, social and societal factors.[21–23] They have short-term and long-term influences on health promotion and disease prevention, while it is very probable that they will continue or shape the lifestyle behaviors adopted during adulthood.[22]

Hence, the aim of this study is the assessment of opinions and behaviors related to healthy lifestyle and cancer prevention among Romanian university students.

Materials and Methods

Study Sample and Procedure for Data Collection

A cross-sectional study was performed during April and May 2017 and involved 400 university students from the four main universities from Cluj-Napoca—a big university city situated in northwest Romania (University of Medicine and Pharmacy and other three universities who have several faculties, except Medicine and Pharmacy). It used an anonymous questionnaire investigating several issues related to lifestyle.

A convenient sample of students was randomly chosen from eight dorms belonging to the four main universities of the town. This approach was used in order to have access to students from different faculties from the four universities, while contact with those students during their activities in the universities had several logistical constraints. One hundred students (50 girls, 50 boys) living in the selected dorms were randomly chosen from each university.[24]

Students were contacted directly in the dorms by a member of the research team and were informed about the voluntary participation and characteristics of the study. The refusal rate was below 6% and the students who refused to participate were replaced with students from the same university, living in the same dorm. The participating students filled in the questionnaires which were collected by members of the research team from each room approximately one hour after their distribution.[24]

The study is part of a research project which received the ethical approval of the Ethics Board of University of Medicine and Pharmacy from Cluj-Napoca, Romania.

This study was conducted in accordance with the Declaration of Helsinki.

Instrument for Data Collection

The study used an anonymous questionnaire developed and tested in previous studies from Romania[11,12] based on data from literature.[1,3,25,26] The present study includes information collected through the anonymous questionnaires with regard to sociodemographic characteristics (age, gender, and university), declared weight and height, opinions and behaviors related to cancer prevention.

The investigated behaviors included:

Consumption of Fruits and Vegetables

It was investigated through two questions regarding how many days they consumed fruits and vegetables fresh or in different meals in the last week, respectively, how many portions of fruits and vegetables they consumed in those days. One portion represents the equivalent of approximately 80 g; for fruit, a serving was defined as a whole fruit (eg, medium apple), three-quarters of a cup (178 mL) of fruit juice, or half a cup (120 mL) of cut-up fruit. For

vegetables, a serving is defined as one cup (240 mL) raw leafy vegetables (eg, lettuce), half a cup of other vegetables, or three-quarters of a cup of vegetable juice.

Consumption of Red Meat

It was investigated through two questions regarding how many days they consumed red meat such as beef, pork, lamb, and goat from domesticated animals including that contained in processed food such as sausages, salami, respectively how many portions of red meat consumed in those days. One portion of red meat was defined as a piece of red meat having approximately the size of a deck of cards (around 90–100 g).

Alcohol Consumption

It was investigated through two questions regarding how many days they consumed alcoholic drinks in the last week, how many drinks were consumed in those days. One portion was defined as one glass of beer (350 mL), one glass of wine (150 mL) or one glass of spirits (40 mL), representing the equivalent of around 10–15 g of ethanol.

Involvement in Physical Activity

Participants were asked about the number of days when they were involved in vigorous physical activity (refer to activities that take hard physical effort and make you breathe much harder than normal, such as aerobics, running, fast bicycling, or fast swimming, carrying heavy loads), moderate activity (refer to activities that take moderate physical effort and make you breathe somewhat harder than normal, such as carrying light loads, bicycling at a regular pace, cleaning the house), walking in the last week and how long (in minutes) was the duration of vigorous activity, moderate activity and walking.[25]

Opinions regarding cancer prevention assessed if participants were aware of the relationship between body overweight, vegetables and fruits consumption, red meat consumption, physical activity, alcohol drinking and cancer prevention using a five-point scale for possibilities of answers (from "I totally disagree" to "I totally agree").

Moreover, students were asked their opinion about the quantity of fruits and vegetables and red meat consumed in the last week (possibilities of answers being appropriate, too much, too less, I do not know) as well as their opinion about their weight (possibilities of answers being appropriate, too big, too low, I do not know) and if they have tried to lose or gain weight in the last year.

Data Analyses

The body mass index (BMI) was computed using the formula BMI=weight/(heigh × height).[1,3]

We calculated the average number of portions of fruits and vegetables consumed per day and the average number of portions of alcohol that they drank per day by multiplying the number of days/week with the number of portions consumed during those days and dividing by seven. At the same time, the average number of portions of red meat consumed per week was computed by multiplying the number of days/week that they consumed it with the number of portions consumed on those occasions.

The number of minutes per week of moderate physical activity (PA) was calculated by summing the number of minutes of intense and moderate PA as well as walking per week. Similar to other studies,[3,25] we considered that 30 min of vigorous physical activity were equivalent to 60 min of moderate physical activity.

The prevalence of the investigated cancer-related behaviors—BMI, consumption of fruits and vegetables, consumption of red meat, involvement in physical activity and drinking alcohol— was assessed and the 2018 WCRF/AICR Score was used to operationalizes the five behaviors. Two of the behaviors addressed by the 2018 WCRF/AICR Score (limit consumption of "fast foods" and other processed foods high in fat, starches or sugars, and limit consumption of sugar-sweetened drinks) could not be included because the questionnaire did not include information about them. The behavioral score was created for each person by summing the score obtained for the five behaviors.

The factor analysis using the method of principal components with unrotated factor solution was used to recognize major structures regarding cancer prevention-related behaviors (the targeted issues were BMI, consumption of fruits and vegetables, consumption of red meat, physical activity, and alcohol use). Similar to other studies, we considered that the main structures referred to factors with eigenvalues of over 1.5.[22,23] The regression method was used to measure the scores of factors for every pattern and for each person.

The frequency of the opinions regarding the role of nutrition and physical activity was assessed. The opinion scores were computed by summing the score obtained by one person for all five investigated opinions. Moreover, the level of acknowledgement of the behavioral mistakes was assessed among those with higher BMI, inappropriate consumption of fruits and vegetables as well as red meat.

Pearson's correlation was used to assess the association between opinion scores, age, gender and the university (participants from the University of Medicine and Pharmacy vs the other students). Moreover, Pearson's correlation was used to evaluate the association between the behavioral score, age, gender, university as well as the opinion scores. At the same time, a similar approach was used for investigating the association between the main cancer prevention-related structures and the variables mentioned before.

Data analysis was performed with SPSS-20 statistics program. Statistical significance is reported at $p<0.05$.

Results

Nutritional Patterns and Physical Activity

As presented in Table 1, 20.8% of the students are overweight/obese, while around 5% are underweight. The majority of the students fulfill the recommendations for physical activity of minimum 150 min per week.

Almost all participants do not respect the recommendations of eating a minimum 400 g of fruits and vegetables and 70% eat even less than half of the recommended quantity. In contrast, almost half of the students eat more than the recommended quantity of 500 g/week of red meat. With regard to alcohol consumption one out of three do not respect the recommendations (maximum one drink/day for women and two drink/day for men).

The factor analyses reveal two factors with regard to cancer prevention-related behaviors. The first one consists of those having an appropriate body weight, and having a higher tendency for consumption of fruits and vegetables, performing physical activity, while being more prone not to respect the recommendations regarding the alcohol consumption. In contrast, the second factor refers to a higher tendency to respect the recommendations both for alcohol and red meat consumption (see Table 2).

Table 1 Nutritional Patterns and Physical Activity

Issues	Percentage %	2018 WCRF/ AICR Score Mean (SD)
BMI[a]		0.41 (0.15)
<18.5 (underweight)	5.7	
18.5–24.9 (normal weight)	73.5	
25–29.9 (overweight)	19.3	
≥30 (obesity)	1.5	
Physical activity[b]		0.84 (0.35)
<75 min/week	14.2	
75-<150 min/week	2.7	
≥150min/week	83.1	
Fruits and vegetables consumption[c]		0.08 (0.13)
≤200 g/day (2.5 portions)	69.5	
>200 g/day and <400 g/day	27.9	
≥400 g/day (5 portions)	2.6	
Red meat consumption[d]		0.26 (0.24)
≤500 g/week (5 portions)	52.7	
> 500 g/week	47.3	
Alcohol consumption[e]		0.64 (0.36)
0 drinks	45.7	
≤1/2 drinks/day (1 for women, 2 for men)	16.1	
>1/2 drinks/day (1 for women, 2 for men)	38.2	

Notes: [a]Coded according to 2018 WCRF/AICR Score as ≥30 or <18.5=0; 25–29.9=0.25; 18.5–24.9=0.5; information about waist circumference was not available. [b]Coded according to 2018 WCRF/AICR Score as <75 min/week=0; ≥75 and <150 min/week=0.5; ≥150min/week=1. [c]Coded according to 2018 WCRF/AICR Score as≤200 g/day=0; >200 g/day and <400 g/day=0.25, ≥400 g/day (5 portions) =0.5; information about the quantity of fiber/day was not available. [d]Coded according to 2018 WCRF/AICR Score as >500 g/week=0; ≤500 g/week=1; *information regarding the consumption of processed meat was not available. [e]Coded according to 2018 WCRF/AICR Score as >1/2 drinks/day=0; ≤1/2 drinks/day=0.5; 0 drinks/day=1.

Nutrition, Physical Activity and Cancer Prevention: Participants' Opinions

As presented in Table 3 the majority (81%) of the students are convinced about the role of physical activity in cancer prevention and 73% recognize the role of alcohol consumption in cancer development.

Around 73% are convinced about the role of fruits and vegetables in cancer prevention, while one quarter does not know. Moreover, among those who do not eat enough portions of fruits and vegetables 44.5% believe that the consumed quantity is enough.

Only around one third know about the relationship between red meat consumption and cancer risk, while almost half recognize their lack of knowledge regarding this. At the same time, only 10.5% of those eating too much red meat are aware of this fact.

Fewer than two thirds of students are convinced about the relationship between excessive weight and cancer. The

Table 2 The Main Structures Regarding Cancer Prevention-Related Behaviors: Results of Factor Analyses[a]

Issues	Factor 1	Factor 2
BMI	0.71	
Physical activity	0.68	
Fruits and vegetables consumption	0.30	
Red meat consumption		0.78
Alcohol consumption	−0.34	0.64

Notes: [a]Factor loadings higher than 0.30 are depicted.

percentage of those who realized that they are overweight is 65% and 62% of the overweight are trying in the last year to lose weight.

Associations Between Opinion Score, Behavioral Score and Other Variables

The results of the bivariate correlation show that the opinion score was not influenced by age, gender or university, while the behavioral score was higher among girls and those with higher opinion scores. Similar situation was encountered for factor 2, while factor 1 was associated with being students at the University of Medicine and Pharmacy (see Table 4).

Table 3 Opinions About Cancer Prevention [a]

	I Totally/I Partially Agree %	I Do Not Know %	I Totally/I Partially Disagree %
High body weight could increase the risk of cancer	60.7	30.7	8.6
Physical activity could contribute to cancer prevention	81.5	17.0	1.5
Consumption of fruits and vegetables could contribute to cancer prevention	71.3	24.4	4.3
Consumption of red meat could increase the risk of cancer	36.6	47.7	15.4
Alcohol consumption could increase the risk of cancer	73.1	16.2	9.9

Notes: [a]Answers were coded as I totally disagree= −2, I partially disagree= −1, I do not know= 0, I partially agree= +1, I totally agree= +2.

Table 4 Association Between Opinion Score, Behavioral Score and Other Variables: Results of Bivariate Correlation Analyses[a]

	Opinion Score	Behavioral Score	Factor 1	Factor 2
University[b]	NS	NS	0.160	NS
Gender[c]	NS	0.286	NS	0.337
Age	NS	NS	NS	NS
Opinion score	–	0.172	NS	0.202

Notes: [a]Only Pearson coefficients of correlations which are significant are depicted. NS, non-significant. [b]Coded as 0=other universities, 1=University of Medicine and Pharmacy. [c]Coded as 0=boys, 1=girls

Discussion

This study presents data on the opinions and behaviors of Romanian students with regard to lifestyle and cancer prevention.

The results show that the relationship between being overweight and several types of cancers was recognized by 60% of the students. Another Romanian study performed in 2011 among adults having relatives with cancer showed that the fact that being overweight might increase the risk for several cancers was recognized by 45% of the participants, with people from urban areas being more aware of this.[12] One out of five university students from our study were overweight or obese, with obesity being present among fewer than 2% of the participants. Another study performed in 2016 among Romanian university students showed similar results, while the prevalence of being overweight/obese was more than double among older adults, as proved by another Romanian study.[11,22] Moreover, in our study two thirds of overweight students recognize that their weight is higher than it should be and 62% were trying to lose weight in the last year, showing the need for appropriate education and counselling measures and services for body weight management among university students.

A percentage of 71% of our study participants recognized the protective effect of fruit and vegetable consumption against cancer; similar results were obtained by the previous study performed among Romanian adults having relatives with cancer.[12] Nevertheless, almost all do not fulfil the recommendations of eating 400 g fruits and vegetables daily and two thirds are eating less than 200 g per day. One reason might be the fact that they do not know the recommendations, almost half of the participants believing they eat enough. Other studies from Romania

also underlined the insufficient amount of fruits and vegetables consumed by different population groups, calling for research and health promotion measures in order to increase fruits and vegetables consumption.[11,22,27–29]

The risk of consuming red meat and cancer have got the lowest percentage of people who agree with this (around one third), while almost half recognize that they do not know about this issue. In the study performed among Romanian adults having relatives with cancer half of the participants knew the link between the consumption of red meat and cancer; older people, those with a higher educational level and those living in urban areas were more aware of it.[12] Moreover, in our study 47% of the participants eat more than 500 g of red meat per week; similar results were also found in the study performed among older Romanian adults.[11] As for fruits and vegetables, one reason might be the fact that they do not recognize the recommendations, only 10% of those eating too much recognize this. Once again, our study shows that these recommendations for limiting the consumption of red meat remain insufficiently known by several population groups and as a consequence lead to overconsumption by many participants. This situation is influenced by other factors such as gastronomic cultural habits and accessibility (pork is traditionally the meat most frequently consumed in this region of Romania, while the accessibility and attractiveness because of price, taste, ease of use of different processed meat products such as salami, sausages is also high).[22,27]

With regard to the risk of alcohol consumption for different types of cancer 73% recognize this, the percentage being similar to that obtained among adults having relatives with cancer.[12] Thirty-eight percent of the students drink more than the recommended portions of drinks/day, the percentage being higher compared with results performed among older adults.[11]

The protective effect of physical activity for cancer was admitted by the majority of students (81.5%), the percentage being higher than in the study performed among adults having relatives with cancer where this relationship was recognized by two thirds of the study sample, people from urban areas and those having a higher educational level being more aware.[12] At the same time, more than 80% of the students respect the recommendations of physical activity/week, which is the strength of this population group, while other groups of adults perform less with respect to this issue.[11] The importance of PA for prevention of chronic diseases was highlighted by different educational activities, including mass media campaigns in Romania, while this age group seems particularly interested in being physically active and fit.

Several studies underline that healthy or unhealthy diet, physical activity, and weight-related behaviors often do not occur in isolation and are correlated with each other in different ways with a possible synergetic effect of multiple health behaviors on the risk of cancer, chronic conditions and other health outcomes.[22,30,31,32]

Our study shows that there are two factors with regard to cancer prevention-related behaviors. The first one comprises having an appropriate BMI as well as having better consumption of fruits and vegetables and performing the recommended time for PA, but these combine with a tendency for inappropriate alcohol consumption. The other factor refers to having a stronger tendency to respect the recommendations regarding red meat consumption and alcohol consumption.

No age and gender differences were found with regard to opinion scores, but girls scored higher with regard to behavioral score and it is noticed that the tendency of belonging to the female group is associated with factor two.

Students from the University of Medicine and Pharmacy did not score higher for opinions or behavioral scores, but factor one was more frequent among this group. Students with higher opinion scores had also a higher behavioral score and were more frequent among the group from the factor two.

This study is subject to several limitations: it has a cross-sectional design and a limited sample of Romanian university students from Cluj-Napoca, some of the information from the 2018 WCRF/AICR Score was not evaluated by this study performed in 2017, while weight and height were not measured and rely on students' own perception.

Conclusions

This is the first study from Romania looking into knowledge, attitudes and behavior of students with regard to the role of diet and physical activity for cancer prevention. It underlines that this group has good level of knowledge with regard to the importance of some factors for cancer prevention (physical activity, alcohol consumption), but the translation of this knowledge into practice varies, with involvement on PA being the recommendation best

accepted. The level of knowledge for the role of alimentary habits is moderate for fruits and vegetables (they recognize their importance, but do not know how much they should eat) or even low for red meat consumption. Nevertheless, the recommendations are not respected by many students with regard to these two alimentary behaviors. The role of BMI is recognized to quite a high extent and students are preoccupied by maintaining an appropriate BMI, with one out of five being overweight, while many of these overweight students are trying to lose weight.

Compared with older Romanian adults, university students seems to perform better with regard to PA involvement and BMI, similarly with regard to fruits and vegetables consumption and red meat consumption and worst regarding drinking alcohol, possibly related to the developmental phase they are passing through.[11,22,31,32]

Future educational activities should focus on promoting better nutritional habits, decrease alcohol consumption and offer appropriate services for weight management among Romanian university students.

Institutional Review Board Statement

The study is part of a research project which received the ethical approval (120/6.03.2015) of the Ethics Board of University of Medicine and Pharmacy from Cluj-Napoca, Romania.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Students who did not want to participate did not fill in the anonymous questionnaire.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Actual Weight, Perceived Weight and Desired Weight of Romanian School Children by Parents and Children

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Abstract: *Background and Objectives:* The perception of the body weight by children and parents influences the consequent actions undertaken for children's body weight management. This study investigated the correspondence between objective evaluations of Romanian school children (actual weight) and perceptions about weight (perceived weight), preoccupation with body weight management (desired weight) and parents' perceptions on children's weight. *Materials and Methods:* A cross sectional study was performed among 344 children aged 11 to 14 and 147 parents from Cluj-Napoca, Romania. We made anthropometric measurements of children, and short questionnaires were completed by the children and the parents. *Results:* The results show that 3.8% of children were underweight, 68.3% had a normal weight and 27.9% were overweight. Of this sample, 61.5% of underweight children, 20% of normal weight children and 43.7% of overweight children had misperceptions about their weight. The percentage of parents who did not estimate their children's weight correctly was 50%, 11.9% and 41.5%, respectively, for each of the three weight groups. The results of the logistic regression analyses showed that several factors were associated with the misclassification of their own body weight by the children, such as body mass index, gender, weight management practices, misclassification by the parents as well as parent–child discussions on these issues. *Conclusions:* Education for both Romanian parents and children is needed with regard to correctly identifying and managing children' body weight.

Keywords: body weight; misperception; children; parents; weight management

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1. Introduction

Children's body weight has important short and long-term consequences on their health, social and psychological development [1,2]. Underweight is mainly a consequence of inadequate diet and frequent infections, leading to deficiencies in calories, proteins, vitamins and minerals [3]. On the other hand, childhood overweight and obesity can be linked to several medical conditions such as metabolic, cardiovascular, orthopedic, neurological, hepatic, pulmonary, and renal disorders. Moreover, it can affect social and emotional health, as well as academic performance [1,2] especially since the overweight child is likely to continue to be overweight at adulthood [3].

The perception of the body weight by children and parents influences the consequent actions undertaken for the children's body weight management [4–10]. The children's perception of body weight determines the quantity and quality of food intake, body weight management practices and communication with parents, friends and health professionals on this issue [5–7]. The parents' perception of the children's nutritional status contributes to the pattern of care that includes in-house feeding practices, shaping daily eating habits, and seeking professional help when needed [8–10].

Misperceptions of the children's body weight by both the children and the parents might lead to unhealthy eating habits and inappropriate actions for combating overweight or underweight, while there is also concern that focusing excessively on a child's weight could foster the development of body image problems, mental health issues and disordered eating [6–10]. The challenge is to assess the children's and parents' perceptions of the real weight of the children and to correct misperceptions, applying educational interventions for appropriate children's body weight management.

Studies performed in several countries that proved that misperceptions regarding body weight as well as body dissatisfaction among children is influenced by several individual, familial and social factors, such as residence, age, gender, socio-economic factors, lifestyle-related behaviors, mental wellbeing, familial opinions and practices related to eating habits and weight management, communication with peers and family, media messages, and health promotion actions, and might suffer differences between countries, making it important to perform studies which identify these issues in different population groups from different countries [9–19].

In Romania, several studies have focused on different groups of children's and adolescents' body weight measurement [18–21]. In 2017/18, study about health behavior in school aged children investigated the prevalence of overweight and obesity, as well as underweight and body image among school children aged 11, 13 and 15 from Romania, but no objective measurements were made, with the data relying on the children's declarations regarding their own height and weight. The results showed that among girls, overweight (including obesity) was 22% (for 11-year-olds), 15% (both among 13- and 15-year-olds), while among boys the results were 32%, 30% and 27%, respectively, for the three age groups. Underweight varied between 4–6%, both among girls and boys of different ages. The percentage of girls who thought they were too fat varied between 24 % among 11-year-olds to 34% among 15-year-olds, while among boys the percentage was 25% among 11-year-olds, 24% among 13-year-olds and 21% among 15-year-olds [18].

To the best of our knowledge, no study has investigated yet the correspondence between the objective evaluation of the Romanian children's weight and its perception by children and parents.

This study had three objectives. First, it aimed to determine the correspondence between anthropometric evaluations of Romanian children (actual weight) and their perceptions on weight (perceived weight) as well as their preoccupation with body weight management (desired weight). Second, it investigated the correspondence between the actual weight of Romanian children and the parents' perception of children's weight. Third, it assessed the differences between children who estimated their weight correctly and those who estimated it inappropriately.

2. Materials and Methods

2.1. Study Design and Sample

We performed a cross sectional study in 2 schools from Cluj-Napoca, a town with more than 300,000 inhabitants from north-west Romania in the period March-May 2013. Approval for the study was obtained in December 2012 from the review committees formed by school directors and teachers of the two schools, according to the standard procedure in Romania at that time. A member of the research team had meetings with the representatives of the schools, presented the objectives, characteristics and tools of the project, which entailed assessing children's physical development through anthropometric

measurements, as well as the evaluation through questionnaires of opinions and practices with regard to their body weight among school children and opinions regarding the body weight of their children among the children's parents. The representatives of the schools gave permission and made the logistical arrangements for the implementation of the project in schools.

The sample included 344 school children (169 girls and 175 boys) aged 11–14 years from all classes from grades V to VII from two schools. All students present in the class during the days when the study was performed were included in study.

Children were informed that the study involved anthropometric measurements (weight and height) and filling in by them of short questionnaires. At the same time, it was clearly specified orally as well as in written at the beginning of the questionnaire that their participation was voluntary, while all the data would be confidential, with only the research team having access to the collected information. School children could refuse to participate by not filling in the questionnaire, while filling in the questionnaire was an informed consent for their participation. No refusal was recorded. All students filled in the questionnaires and after that the anthropometric measurements were performed.

The parents of the participating students were also invited to participate by filling in a questionnaire sent through letters. Similarly to the questionnaire for the children, it clearly specified the voluntary and confidential nature of data collection.

2.2. Instruments for Data Collection

Anthropometric Measurements

Children were evaluated through anthropometric measurements Height and weight were measured in the class by student dieticians. Weight was measured in minimal clothing, without shoes, to the nearest 0.1 kg, with an electronical step scale; height was measured to the nearest 0.5 cm in the same conditions using a stadiometer.

Questionnaires

Children were asked to fill in a short questionnaire assessing their demographics characteristics (age, gender, school) as well as opinions and practices with regard to their body weight:

- Perceived weight—children were asked how they considered their weight, the possible answers being normal, too low, too big. A similar approach was used by other studies, too [10–13,15,18,19].
- Weight management practices in the last year (attempts to lose weight, nothing or attempts to gain weight in the last year);
- Types of methods used in the last year for losing weight if they had tried to do this (children could choose from sport, dieting, consumption of special tea, use of medicine, vomiting, and massage);
- If they discussed about their weight with their parents in the last year (yes/no)
- If they discussed issues focused on their weight with health professionals in the last year (yes/no)

Short questionnaires for parents were sent and returned through letters delivered through the children. The questionnaires assessed the opinions of parents regarding the weight of their children—perceived weight (normal, too low, too big)—and if they discussed issues related to their children's weight with health professionals in the last year.

2.3. Data Analyses

Body mass index (BMI) was calculated from weight and height measurements, based on the following formula: BMI = weight (kg)/height $(m)^2$. Normal nutritional status, underweight, overweight, obesity were established based on the World Health Organization (WHO) recommendations regarding BMI for age and sex (z-scores). Overweight: > +1SD (equivalent to BMI 25 kg/m^2 at 19 years); obesity: > +2SD (equivalent to BMI 30 kg/m^2 at 19 years); thinness: < −2SD [22].

The prevalence of the investigated issues was calculated. Correct/incorrect estimation of actual weight was estimated as follows:

- If children with normal BMI declared that they considered their weight normal they had correct estimation; if they said it was too big or too little they had incorrect estimation (overestimation, underestimation, respectively).
- If children with overweight/obesity said that their weight was too high they had correct estimation, if they considered it normal they had incorrect estimation (underestimation).
- If underweight children said their weight was too little they had correct estimation, if they said it is normal they had incorrect estimation (overestimation).

Logistic regression analysis was performed in order to assess the factors associated with higher BMI (coded as 0—normal weight, 1—overweight, including obesity), with the independent variables being age, gender, estimation of children's weight by children and parents, respectively (both variables were coded as 0—incorrect estimation, 1—correct estimation), the presence of attempts to decrease/increase their weight in the last year (0—no, 1—yes), the presence of discussions between children and parents, respectively, and health professionals with regard to their weight, as well as between parents and health care professionals (0—absent, 1—present).

On the other hand, logistical regression analyses were also used in order to assess differences between children with normal weight who estimated their weight correctly and those who underestimated or overestimated, it as well as between children with overweight who correctly estimated and those who underestimated their weight. Dependent variables were coded as 0—incorrect estimation (overestimation or underestimation), 1—correct estimation. The independent variables for all these logistic regression analyses were age, gender, the presence of attempts to decrease/increase their weight in the last year (0—no, 1—yes), the presence of discussions between children and parents, respectively, with health professionals with regard to their weight, as well as between parents and health care professionals (0—absent, 1—present), estimation of children weight by parents (coded as 0—incorrect estimation, 1—correct estimation). Due to the small sample, a similar analysis was not possible among children with underweight.

Statistical analyses were performed using IBM SPSS Statistics for Windows Version 20 program. Statistically significant results are reported at $p < 0.05$.

3. Results

3.1. Actual Weight, Perceived Weight and Desired Weight among School Children

The objective measurements of body weight showed that out of the school children, 3.8% were underweight, 68.3% had a normal weight and 27.9% were overweight (including obesity) (see Table 1).

Regarding perceived weight, only 38.5% of the underweight children recognized this, while the others considered they had a normal weight. Among normal weight children, the majority correctly estimated their weight, 11.1% considered they were underweight and 8.9% believed there are overweight. The percentage of overweight children who correctly estimated their weight was 56.2%, while the others thought their weight was normal.

The desired weight results showed that 61.5% of the underweight and 17.9% of the normal weight children tried to gain weight in the last year, while 82.7% of the overweight children and 31.9% of the normal weight children tried to lose weight in the last year. The respective methods used for losing weight among overweight children and children who had normal weight and declared attempts to lose weight in the last year were as follows: sport (80.1% and 84%), dieting (52.6% and 42.7%), consumption of special tea (3.2% and 0%), use of medicine (1.9% and 1.3%), vomiting (0.6% and 0%), and massage (1.3% and 0%).

The percentage of children who declared talking with their parents in the last year about their weight increased from 58.3% among underweight children to 73.2% among normal weight children and 84.7% among overweight children. The discussion with a health care professional in the last year concerning their weight was reported by 38.5% of

the underweight children, 32.3% of the normal-weight children and 43.9% of the overweight children.

A total of 147 parents of the investigated children (85% women and 15% men) filled in the questionnaire. The parents correctly appreciated the weight of their children in half of the cases of underweight children, 88.1% of normal weight children and 59.5% of overweight children (see Table 1). Half of the parents of underweight children and around 40% of the overweight children misperceived their child's weight as normal. Among normal weight children's parents, 9.9% misperceived their child's weight as too low and 2% appreciated it as too high.

Around half of the parents of children with underweight or normal weight and two thirds of parents having overweight children reported discussions with a physician in the last year focused on the child's weight.

3.2. Factors Associated with Overweight

Table 2 shows that in comparison with children with a normal BMI, those with a higher BMI were more frequently boys and had a tendency to underestimate their weight, while their parents also did this. At the same time, they declared more frequent attempts to lose weight in the last year, and had more frequently discussed about their weight with their parents and health professionals in the last year, while their parents were more eager to bring up this issue during discussions with health professionals.

Table 1. Actual weight, perceived weight and desired weight among Romanian school children.

	Actual Weight		
	Underweight	**Normal Weight**	**Overweight**
	n = 13%	*n* = 235%	*n* = 96%
Perceived weight by children			
Underweight	38.5	11.1	0.0
Normal weight	61.5	80.0	43.7
Overweight	0.0	8.9	56.3
Desired weight by children			
Attempts to lose weight	0.0	31.9	83.3
Attempts to gain weight	61.5	17.9	0.0
None of the above	38.5	50.2	16.7
Discussion between children and health care professionals	38.5	32.3	42.7
Discussion between children andparents	58.3	73.2	85.4
Perceived weight by parents			
Underweight	50	9.9	0.0
Normal weight	50	88.1	41.5
Over weight	0.0	2.0	58.5
Discussions between parents and health care professionals	50	48.5	68.3

3.3. Factors Associated with Correct, Underestimation and Overestimation of Their Own Weight among Romanian Children

A percentage of 28.2% of the children had an incorrect estimation of their own weight, while 21.1% of the parents had misperceptions regarding their children's weight.

Table 2. Factors associated with BMI, correct, underestimation and overestimation of their own weight among Romanian children [a].

	BMI	Normal Weight Children		Overweight Children
	Overweight vs. Normal Weight OR (95%CI) [b]	**Correct Estimation vs. Incorrect Underestimation OR (95%CI) [c]**	**Correct Estimation vs. Incorrect Overestimation OR (95%CI) [d]**	**Correct Estimation vs. Incorrect Underestimation OR (95%CI) [c]**
Gender				
Girls	0.59 (0.37–0.96) *	2.5 (1.03–6.03) *	0.11 (0.03–0.51) **	1.60 (0.69–3.69) ●
Boys	1	1	1	1
Age	0.95 (0.71–1.27) ●	0.75 (0.45–1.24) ●	0.61 (0.34–1.08) ●	0.91 (0.55–1.62) ●
Weight estimation by children				
Correct	0.32 (0.19–0.53) ***	-	-	-
Incorrect	1			
Attempts to gain weight in the last year [e,f]				
Yes	-	0.05(0.01–0.13) ***	-	-
No		1		
Attempts to lose weight in the last year [g]				
Yes	10.16(5.63–18.34) ***	-	0.24(0.09–0.62) **	7.62(2.00–29.97) **
No	1		1	1
Discussion between children and parents				
Yes	2.02 (1.08–3.77) *	0.21 (0.05–0.95) *	1.96(0.78–4.92) ●	3.90(1.12–13.51) *
No	1	1	1	1
Discussion between children and medical professionals				
Yes	1.63 (1.01–2.65) *	0.95 (0.40–2.25) ●	2.14(0.69–6.63) ●	1.40(0.61–3.18) ●
No	1	1	1	1
Weight estimation by parents				
Correct	0.19 (0.08-0.46) ***	10.1 (2.34–40.79) **	2.58 (0.44–14.98) ●	7.20 (1.78–29.01) **
Incorrect	1	1	1	1
Discussion between parents and medical professionals				
Yes	2.12 (1.01–4.49) *	0.45 (0.12–1.62) ●	1.44 (0.43–4.80) ●	2.88 (0.74–11.20) ●
No	1	1	1	1

[a] The table depicts the results of logistic regression analyses; [b] BMI coded as 0-normal, 1- overweight; [c] Coded as 0-incorect underestimation, 1- correct estimation; [d] Coded as 0-incorect overestimation, 1-correct estimation; [e] Overweight children did not declare attempts to gain weight in the last year; [f] Normal weight children who considered their weight to be high did not declare attempts to gain weight in the last year; [g] Normal weight children who considered their weight to be low did not declare attempts to lose weight in the last year; ● $p > 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

As Table 2 shows, in comparison with normal weight children who misperceived their weight as low, normal weight children who correctly estimated their weight were more frequently girls and were less likely to declare attempts to gain weight as well as less likely to report that they talked with their parents about their weight; correct estimation of their own weight by the children was associated with higher correct estimation of their children's weight by parents.

On the other hand, in comparison with normal weight children who misperceived themselves as having a higher weight than their actual one, normal weight children who correctly estimated their weight were more frequently boys and were less likely to attempt weight loss, but no difference was found between the two groups with regard to the perceptions of their parents (see Table 2).

Table 2 presents that, among overweight children, in comparison with those who incorrectly considered their weight as normal, the children who correctly estimated their weight were more likely to try to lose weight and to talk with their parents about this issue. At the same time, the correct estimation of their own weight by overweight children was associated with higher correct estimation of the children's weight by their parents.

4. Discussion

This study focuses on assessing the actual weight, as well as perceived weight and desired weight of Romanian school children. The results show that more than one quarter of the children are overweight, while only 4% are underweight, with boys having a higher risk for being overweight. The results are similar to those from other Romanian studies which used anthropometric measurements [20,21], and one has evidenced the increasing prevalence trend of overweight children in a pooled analysis of cross-sectional studies between 2006 and 2015 [21]. The prevalence of underweight children was similar to that in our study (4%), while that of overweight (including obese) children was 28.3%. Male gender compared to female, prepubertal age compared to post pubertal age and urban environment had higher risk for overweight [21]. A survey performed in Bucharest, the capital of Romania, among school children aged 6–18 showed a prevalence of 31.6% overweight (including obese) based on WHO standards [20].

Research in the field of the lifestyles of children is time and energy consuming process, but definitely also a rewarding one, since the results are important pillars for designing appropriate health promotion interventions [23]. In Romania, no study has yet investigated the correspondence between the objective evaluation of secondary school children's body weight and its perception by children and parents. The results of our study showed that 28.2% of the children had an incorrect estimation of their own weight, with overweight children being more prone to have incorrect estimation of their own weight in comparison with the children with normal weight. Studies performed in United States of America, Australia and other European countries showed a prevalence of incorrect estimation of their own weight by children and adolescents varying between 29% and more than 40%, depending on the country, age and BMI [11–15]. Several studies also showed a higher tendency of overweight children than normal weight children to misclassify their own weight [11–13].

In our study, we identified several misperceptions regarding their weight among all three BMI groups. The percentage of underweight children was low, but two thirds of them considered their weight as normal. Nevertheless, two thirds of the underweight children have tried to gain weight in the last year, showing a preoccupation with having a higher desired weight. It might be possible that these attempts led to a certain increase in weight and, because of missing appropriate knowledge and skills to correctly appreciate the weight, this made children think that their weight had reached normal levels.

Among normal weight children, the majority recognize their real weight, but one out ten children misperceived it as overweight and one third reported that they had tried to lose weight in the last years. This misperception was more frequent among girls and was associated with a greater tendency to try to lose weight. These data show the tendency of

some children to have unrealistic expectations regarding the need to lose weight, either because they misjudge their weight or because they want to lose weight, despite the fact that they see their weight as normal. It is probably a consequence of several media and peer messages portraying beauty through images of slim persons and encouraging the idea of being slim as a socially desired norm [24–27].

On the other side, one in ten normal weight children think their weight is too low, while 18% of the children have tried to gain weight in the last year. Children with this misperception were more likely to try to gain weight. This situation could be the consequence of the fact that children do not have the ability to appreciate the optimal weight and could do so by visual comparisons with other children, while in several Romanian families, parents have constant concerns about feeding their children enough food, without sufficient knowledge of what the proper nutrition of their children means in terms of food quantity and quality [19].

Almost half (43.8%) of the overweight children did not recognize their abnormal nutritional status, thinking that their weight was normal. No age or gender differences were found with regard to correct estimation of their own weight among overweight children. Nevertheless, 82% of the overweight children in our study have tried to lose weight, mainly by sport and dieting, with overweight children who correctly estimated their weight being more likely to do this. The study did not investigate in detail the change in the body weight after these attempts to lose weight, or if the attempts were correct, serious and with results, but the data underlines that these students need to have a structured health promotion program which educates them on correct nutrition and exercise habits, supports them to set and work towards realistic goals with regard to losing weight, and teaches them how to maintain their real progress.

At the same time, our study showed that 21.1% of the parents did not correctly estimate the weight of their children; again, this situation was more frequent among the parents of overweight children in comparison with those with normal weight. Studies from other studies highlighted that parents' misperceptions regarding the weight of their children vary depending on country/region, their children's age group, the actual weight of children and the time when the study was performed, with several studies showing that these misperceptions are more likely among the parents of overweight children [28–34]. For instance, a large study from Australia showed that one quarter of mothers misclassified the weight of their 14 years old children, while a—country European study showed that 27.6% of parents of overweight/obese children underestimated their children's weight status [5,7].

Parents' underestimation of their child's weight is due to the fact that some of them do not have a clear definition of what overweight means—they might have limited information from health professionals or even tend not to believe in physician/clinical charting of weight and BMI percentiles and estimate the weight through visual comparison with other children Another reason for weight status misclassification could be that the parents are aware of their child's weight, but due to social undesirability, they do not wish to label their children as overweight [5,34]. There are some parents who recognize their child's weight, but others may feel embarrassed to discuss their child's overweight or obesity and may feel reluctant in seeking the advice of a health care professional [5,34]. In our study, both among normal weight and overweight children, those who correctly estimated their weight also more frequently had parents who did so in comparison with those who underestimated their weight.

Communications between children and parents, as well as between children and parents and health professionals with regard to children's weight is an important step in order to identify and correct misperceptions and adopt healthy lifestyle behaviors which contribute to the prevention and correction of underweight and overweight [32,35]. In our study all these forms of communication were more frequent among overweight children in comparison with normal weight children. Moreover, among normal weight children the discussions with parents were reported more frequently by children with incorrect

underestimation of their weight, while among overweight children the discussion with parents on this issue were more frequent among those who correctly estimated that their weight was too high. Similarly to studies from other countries, these data suggest that if parents fail to correctly estimate the weight of their children, it is unlikely they will recognize the importance of interventions targeting the promotion of healthy nutrition and body weight management [5,32–35].

The current epidemiological context with online schooling, inadequate physical activity and sedentary behavior in response to COVID-19 pandemic, may lead to an increased risk of childhood obesity [36]. Although data collection from our study predates the COVID-19 pandemic, these results and subsequent parent and child-based educational interventions, reset in this long-term epidemiological context, could positively influence children's COVID-related weight gain due to the switch to online learning and improve their nutritional status recognition. Healthcare professionals should share their recommendations with both parents and children for weight gain control, as well as interventions focused on increasing the accuracy of normal weight perception, helping to promote healthy weight loss and maintaining optimal weight [35,36].

This study is subject to several limitations. First, it included a sample of children aged 12–14 from one big city of Romania, but because of logistical and funding constraints it did not include a nationally representative sample, so the generalization of these results beyond this sample is limited Second, similarly to other studies, this is an exploratory study assessing the perceived weight of children based on a question which investigated if children believed their weight was normal, too low or too high; future studies might use more complex scales for assessing this issue. Third, the participation rate of the parents was modest, while the results are based only on the information declared by both parents and children through means of short questionnaires, since the study is an exploratory one. Future studies should try to motivate the parents to participate more and should focus more on details regarding the knowledge, attitudes and practices regarding body weight management both among children and parents. Last, but not least, the study was performed in 2013 and in the last few years, especially during the COVID-19 pandemic, several changes might have happened with regard to opinions and practices regarding weight and weight management both among children and parents in Romania. Nevertheless, this study investigated for the first time in Romania the correspondence between actual weight, perceived weight and desired weight among children and their parents, offering information needed for the activities of health promotion in this field. Moreover, the data made available by this study could be useful for the better assessment and understanding of the changes with regard to this subject over a longer period of time, if future studies should happen to investigate these issues.

5. Conclusions

Our study identified children's and parents' misperceptions about children's weight, having as consequences a lack of parent–child communication about health issues, unhealthy practices for the self-management of weight, delayed addressing of weight-related issues to healthcare professionals and late interventions.

Efforts should focus on developing school based programs which assess children's weight and communicate correctly to both children and parents their nutritional status, as well as actions which should be taken for the appropriate management of children's weight and childhood health promotion. Further studies are needed to explore educational strategies dedicated to both parents and children, focused on optimal recognition and proper management of children's body weight.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the review committees formed by school directors and teachers of the 2 participating schools-School ''Iuliu Hatieganu'' from Cluj-Napoca, Romania and School ''Lucian Blaga'' from Cluj-Napoca Romania on December 2012.The representatives of the schools gave permission and made the logistical arrangements for the implementation of the project in schools, the standard procedure in Romania at the moment when the study was performed.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the first author.

Conflicts of Interest: The authors declare no conflict of interest.

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REVIEW

ROHHAD (Rapid-onset Obesity with Hypoventilation, Hypothalamic Dysfunction, Autonomic Dysregulation) Syndrome—What Every Pediatrician Should Know About the Etiopathogenesis, Diagnosis and Treatment: A Review

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Abstract: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation (ROHHAD) syndrome is a rare disease with unknown and debated etiology, characterized by precipitous obesity in young children, hypoventilation and autonomic dysregulation with various endocrine abnormalities. Neuroendocrine tumors can be associated in more than half of the cases. This rare condition has a severe outcome because of high morbidity and mortality. We provide a comprehensive description of the etiopathogenetic theories of the disease, clinical presentation, diagnostic workup and treatment possibilities.

Keywords: obesity, hypoventilation, hypothalamic dysfunction, autonomic dysregulation

Introduction

Rapid onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) syndrome is a rare disease first described by Fishman et al[1] and renamed ROHHAD by Ize-Ludlow et al in 2007.[2] The acronym ROHHAD describes the typical sequence of symptoms. This disease is characterized by early and rapid onset of obesity associated with hypoventilation, autonomic dysregulation and endocrine abnormalities. The association with tumors with neural crest origin has included the termination NET into the acronym (ROHHADNET).[3–5]

The clinical manifestations of ROHHAD syndrome overlap with those of congenital central hypoventilation syndrome (CCHS) and late-onset central hypoventilation syndrome (LO-CHS). Clear delineation from these entities is provided on genetic basis (mutation of the paired-like homeobox 2B gene *PHOX2B* which is present in patients with CCHS) and the absence of hypothalamic dysfunction in LO-CHS.[6] The diagnosis of ROHHAD syndrome is challenging due to unknown etiology, absence of confirmatory tests and is made based on clinical presentation. The condition is characterized by high morbidity and mortality rates.[4,5]

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Because of global epidemic of childhood obesity, it is very important for every pediatrician to recognize this condition early in order to avoid the complications and ensure a good quality of life for these patients.

Incidence

ROHHAD syndrome is a very rare disorder, about 100 cases being reported to date and it is considered a relatively new disease.[4,5] Because of the explosion of the exogenous obesity in children worldwide, ROHHAD syndrome must be considered for differential diagnosis in obese children.

Etiopathogenesis

Three main etiopathogenetic hypothesis have been postulated: genetic, epigenetic, and autoimmune.

Genetic Theory

Genetic basis of ROHHAD syndrome has been extensively investigated and various studies ruled out the mutations in several candidate genes, including *PHOX2B*, the gene causative for congenital central hypoventilation syndrome and genes responsible for development and function of the hypothalamic, neuroendocrine and autonomic systems. Candidate genes studied and their role in the pathogenesis of ROHHAD syndrome are presented in Table 1.

PHOX2B encodes a transcription factor that has an important role in the regulation of neural crest migration and development of the autonomic nervous system and is considered the disease-defining gene for CCHS. Similarly with ROHHAD syndrome, the CCHS phenotype includes autonomic nervous system dysregulation and endocrine

Table 1 Candidate Genes in ROHHAD Syndrome

Gene	Protein	Function	Associated Diseases	References
ASCL1	Human achaete-scute homolog 1	Regulation of neuroendocrine cell differentiation, development of specific neuronal lineages	Central hypoventilation syndrome, neuroblastoma	16,18
BDNF	Brain-derived neurotrophic factor	Neuronal development, differentiation of selected neuronal populations, synaptic activity, regulation of energy balance, inflammation	Central hypoventilation syndrome, Wilms' tumor, aniridia, genitourinary anomalies, mental retardation	2
HCRT	Hypocretins	Sleep-wake cycle regulation, energy balance, regulation of food intake	Narcolepsy	14
HCRTR1	Hypocretin receptor type 1	Sleep-wake cycle regulation, energy balance, regulation of food intake	Narcolepsy	14
HCRTR2	Hypocretin receptor type 1	Sleep-wake cycle regulation, energy balance, regulation of food intake	Narcolepsy, cluster headache	14
HTR_{1A}	5-hydroxytryptamine (serotonin) receptor 1A	Hypothalamic (appetite control and energy regulation), neural activity, behavior, mood	Periodic fever, generalized anxiety disorder	12
NECDIN	Necdin	Nervous system development, including peripheral autonomic neurons	Prader–Willi syndrome	16,19
NTRK2	Tropomyosin receptor kinase B (TrkB)	Neuronal development, synaptic plasticity	Obesity, hyperphagia, developmental delay, epileptic encephalopathy	20,21
OTP	Orthopedia homeobox	Hypothalamic neuroendocrine cells differentiation	Kwashiorkor, marasmus	12
PACAP	Pituitary adenylate cyclase activating polypeptide	Brain (respiratory, cardiovascular, visceral, thermoregulatory control, energy homeostasis)	Sudden infant death syndrome	12
PHOX2B	Paired-like homeobox protein 2B	Respiratory, development of the autonomic nervous system	Congenital central hypoventilation syndrome, neuroblastoma	2,12
RAI1	Retinoic-acid induced 1	Craniofacial and nervous system development, neuronal differentiation, regulator of the circadian cycle	Smith–Magenis syndrome, alacrimia, achalasia, mental retardation	17

abnormalities, which makes the clinical differentiation very difficult, but consideration of *PHOX2B* as a disease-defining gene for CCHS allows the genetic distinction between the two entities.[2,6–9]

Mutations in the gene of *BDNF* with roles in the neuronal development and the impairment of activation of its receptor TrkB were analyzed in patients with ROHHAD syndrome and obesity and no significant correlation was found.[2,10,11]

Variations of the genes with role in the development of the hypothalamus and autonomic nervous system such as 5-hydroxytryptamine receptor 1A (HTR_{1A}), orthopedia (*OTP*), pituitary adenylate cyclase activating polypeptide (*PACAP*) were analyzed but they were not significantly correlated with ROHHAD syndrome.[12] The absence of hypocretin-1 in the cerebrospinal fluid of a patient with ROHHAD syndrome and narcolepsy was reported, suggesting a causative relation, but other studies demonstrated the absence of mutations in *HCRT, HCRTR1* and *HCRTR2* genes in patients with ROHHAD.[13–15] Mutations in *NECDIN* gene with role in respiratory rhythmogenesis and hypothalamic insufficiency and in *ASCLI* gene, required for the generation of ventral neuroendocrine neurons which acts as potential modifier gene of *PHOX2B* were not correlated with ROHHAD syndrome.[16]

A nonsense mutation was reported in the retinoic acid-induced 1 (*RAI1*) gene known to cause Smith–Magenis syndrome (SMS), in a patient with morbid obesity and clinical diagnosis of ROHHAD syndrome, suggesting a potential overlap with SMS.[17]

Epigenetic Theory

Epigenetic hypothesis is supported by report of discordant presentation of ROHHAD syndrome in monozygotic twins.[15,22] Patwari et al reported a pair of monozygotic twin girls with concordant growth and development until eight years of age and characteristic features of ROHHAD syndrome appearance in the affected twin after this age.[22] The authors highlighted the possibility of variation in the epigenomes of identical twins leading to discordance in phenotypes of twins. Barclay et al did not identify coding differences in the same pair of discordant monozygotic twins.[15]

Immunologic Theory

The immune-mediated pathogenesis has been suggested by several authors who reported patients with clinical presentation consisted to ROHHAD in whose cerebrospinal fluid analysis disclosed an intrathecal synthesis of oligoclonal bands and antihypothalamus and antipituitary antibodies were detected.[23,24] Association with celiac disease, may suggest further evidence for immune-mediated etiology.[25] Autoimmune-mediated process has been illustrated by the positive effect of the intensive immunosuppressive treatment (cyclophosphamide, rituximab, immunoglobulin and corticoids) for the neuropsychological function in four patients with ROHHAD syndrome and ganglioneuroblastoma. In these patients the autoimmune process was considered plausible, given that neuroblastoma is associated with autoimmune-mediated paraneoplastic syndromes, as opsoclonus-myoclonus syndrome.[15,26,27] In another 15-old -year patient with ROHHAD syndrome with focal inflammation in the periaqueductal grey matter and hypothalamus, corticosteroids, immunoglobulins and mycophenolate mofetil long-term administration had a beneficial effect for the neuropsychological function and autonomic disorders.[28] Autopsy findings in six children with ROHHAD syndrome revealed features of encephalitis characterized by lymphocytic infiltrate mainly perivascular, various distributing in the brain, suggesting also the immune mediated pathogenesis.[29]

Clinical Presentation

The onset of this disease ranges from 0 to 9 years, but the most common onset is in early childhood, at ages between two and four years, with hyperphagia and rapid weight gain. Children with ROHHAD syndrome usually have normal growth and development and good general health prior to onset of symptoms. Clinical presentation of these patients is variable in severity and timing.[2,4,5] The clinical presentation is heterogenous, there are cases with marked endocrine involvement, while others exhibit marked behavioral disturbances.

Rapid Obesity

Rapid obesity in early childhood is often the first recognizable sign of the disease.

Hypothalamic Dysfunction

Hypothalamic dysfunction may manifest as growth hormone deficiency, diabetes insipidus, transient syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypodipsia, central precocious puberty, premature adrenarche, amenorrhea, hypogonadotropic hypogonadism, hyperprolactinemia, hypothyroidism, corticotrophin deficiency, low or normal IGF1 level. Dysnatremia

(hypernatremia and hyponatremia) may be present and is linked with impaired water balancing such as polydipsia or diabetes insipidus.[4,5,30,31,34] These manifestations appear from months to years following the rapid-onset obesity.

Autonomic Dysregulation

Autonomic dysregulation may present as ophthalmologic abnormality, such as blurred vision, altered pupil response to light, strabismus, ptosis, altered perception of pain, gastrointestinal dysmotility with chronic constipation or diarrhea, bradycardia, neurogenic bladder, excessive sweating, thermal dysregulation (hypothermia, hyperthermia), cold hands and feet, livedo reticularis, pseudo Raynaud's phenomenon, syncope, urinary incontinence, dysarthria.[4,5,32–34]

Behavioral Disorders

Behavioral change is the most common form of cognitive dysfunction and the symptoms include mood changes such as irritability and aggression, hyperactivity, fatigue, social withdrawal, poor school performance, intellectual disability, flat affect, hallucination, major depressive disorder, anxiety, attention deficit disorder, self-injurious behavior, obsessive-compulsive disorder, oppositional-defiant disorder, bipolar disorder, and psychosis.[4,5,26–28,34]

Neurologic Abnormalities

Neurologic abnormalities consist of seizure, blurring of consciousness, sleep disturbance, hypersomnolence, narcolepsy, developmental delay, developmental regression, gait disturbance, nystagmus, general weakness. Seizures may be related to episodes of hypoxemia due to inadequate ventilator support. Enlargement of the pituitary gland and generalized brain atrophy were also reported.[4,5,34,35]

Hypoventilation

Hypoventilation is the most life-threatening feature of ROHHAD syndrome because it can lead to cardiorespiratory arrest. Most of children with ROHHAD syndrome have obstructive sleep apnea, hypoxemia and hypercapnia at early ages, but in more severe cases hypoventilation can also occur while awake. The spectrum of sleep disorders breathing is completed by central sleep apnea, abnormal ventilatory response to carbon dioxide, nocturnal hypoventilation, and cyanotic episodes. Early recognition of respiratory abnormalities raises the index of suspicion of ROHHAD syndrome.[36,37]

Hypothyroidism, one of the most common associated endocrine disorders can influence the central ventilatory control based on decrease of oxygen consumption.[2,4,5]

Tumors of Neural Crest Origin

Approximately 40–56% of the patients with ROHHAD syndrome develop tumors of neural crest origin such as ganglioneuroma and ganglioneuroblastoma.[3–5] These tumors are localized in the chest, abdomen or along the sympathetic nervous system chain. Hamartomatous masses with neural elements were also reported in one case.[4] Most of the children recorded a short period of time (approximatively two years) between the onset of obesity and the diagnosis of neural crest origin tumor.[5]

Dysmorphic Features

Dysmorphic features as depressed nasal bridge, macrocephaly, anteverted nares and hypertelorism were also described in ROHHAD patients.[32]

Metabolic Disorders

Insulin resistance, impaired glucose intolerance, diabetes mellitus, hypertriglyceridemia and progressive fatty liver disease were reported in several cases.[2,5,38]

Other Clinical Manifestations

Other clinical manifestations may be fever, rash, enuresis, headache, edema, pulmonary hypertension, cough, renal failure, rectal prolapse secondary to dysregulation of the digestive system, scoliosis.[4,5,33] Recurrent upper respiratory tract infections are reported in these children.[39]

Diagnosis

The diagnosis of ROHHAD syndrome is based on clinical presentation and clinical course and involves a cooperative consultation by specialists in the fields of pediatrics, pneumology, endocrinology, oncology, psychiatry, otorhinolaryngology, cardiology, surgery, nutrition, and psychology. There is no genetic testing available to diagnose this disorder.

The diagnosis is made based on the presence of following features: (1) rapid-onset obesity starting in early childhood and alveolar hypoventilation during sleep; (2) signs and symptoms of hypothalamic dysfunction and autonomic disturbances; and (3) exclusion of other condition causing similar features, such as congenital central hypoventilation syndrome. Rapid onset obesity and the most common endocrine disorders such as precocious puberty and hypothyroidism are very often the early recognizable

signs. Sequential comprehensive evaluation is recommended for children with ROHHAD syndrome as the clinical presentation is very variable (Table 2).

Differential Diagnosis

Because of phenotypic similarities, the differential diagnosis of patients with ROHHAD syndrome, typically involves consideration of another disorder marked by early childhood obesity (Prader–Willi syndrome) and a rare disorder with breathing abnormalities and variable features of autonomic nervous system dysregulation (congenital central hypoventilation syndrome). Divergent and similar clinical features of the ROHHAD syndrome, Prader–Willi syndrome (PWS) and congenital central hypoventilation syndrome (CCHS) are presented in Table 3.

Table 2 Evaluation Workup in ROHHAD Syndrome

Clinical Manifestations		Investigations
Obesity		Morphometry Biological and imaging investigations for differential diagnosis
Hypothalamic dysfunction		Hormonal investigations: antidiuretic hormone secretion, IGF-1, thyroid function, prolactin secretion, gonadotropic function, corticotropic function Imaging investigations (ultrasound, MRI)
Hypoventilation		Overnight polysomnography Nocturnal blood gases Pulse oximetry
Autonomic dysregulation	Cardiovascular	Echocardiography 24-h Holter monitoring 24-h arterial blood pressure monitoring Tilt test
	Gastrointestinal	Transglutaminase autoantibodies Gastrointestinal motility studies
	Neuropsychological	Neurocognitive testing EEG
	Ophthalmological	Ophthalmological examination
Neural crest tumors		Abdominal ultrasound Chest and abdominal MRI MIGB I^{123} scintigraphy
Metabolic disorders		Glucose, cholesterol, triglycerides, insulin

Note: Data from these studies.[4,5,32,35,38]
Abbreviations: EEG, electroencephalography; IGF-1, insulin-like growth factor 1; MIGB I^{123}, metaiodobenzylguanidine iodine^{123}; MRI, magnetic resonance imaging.

Treatment

Multidisciplinary care is crucial for the management of these patients, to optimize the quality of life. Another very active and important member of this team is the family. Early diagnosis and adequate conservative intervention are critical for optimizing the quality of life and neurocognitive outcome.

The treatment of ROHHAD syndrome is based on the clinical features (Table 4).

The obesity control based on the strict caloric intake is difficult and requires the intervention of a nutritionist.

Moderate exertion is recommended and pulse oximetry monitoring is required during exercise.

Hypothalamic dysfunction is variable and the treatment may include a strict fluid intake regimen and specific hormone replacement.

Hypoventilation may need artificial ventilation during sleep in the first years of evolution with progressive need for continuous ventilatory support. These procedures, available at home, may improve the quality of life and prevent sudden death.[4,5,36,37] Early recognition of sleep disorders breathing and targeted therapeutic interventions will limit morbidity and mortality associated with ROHHAD syndrome.[36,37]

Autonomic dysregulation may need various therapeutical interventions according to specific symptoms.

Neural crest tumors require surgical removal and multimodal treatment.[4,5]

Complications and Evolution

Insulin resistance, diabetes mellitus, hypertriglyceridemia, progressive fatty liver disease, metabolic syndrome, bradycardia, cor pulmonale, right ventricular hypertrophy, pulmonary hypertension, heart failure and scoliosis have been described in patients with ROHHAD syndrome.[38,39,43,44]

Mortality rate is high at 50–60%, due to hypoventilation, cardiopulmonary failure and cardiopulmonary arrest.[4,5,36]

Conclusions and Key Points

- ROHHAD syndrome is a relatively new disease with multisystemic involvement, with potentially severe evolution. Rapid-onset obesity associated with

Table 3 Clinic and Genetic Diagnostic Criteria in ROHHAD Syndrome, PWS and CCHS

Diagnostic Criteria		ROHHAD Syndrome	PWS	CCHS
Clinical features				
Rapid-onset obesity		Yes	Yes	No
Hypoventilation		Yes	Sometimes	Yes
Hypothalamic dysfunction	Disturbance of maintenance of water balance	Yes	No	No
	Growth hormone deficiency	Sometimes	Sometimes	No
	Hypothyroidism	Sometimes	Sometimes	No
	Hyperprolactinemia	Yes	No	No
	Adrenal dysfunction	Sometimes	Sometimes	No
	Precocious puberty	Sometimes	Sometimes	No
	Hypogonadism	Sometimes	Sometimes	No
Autonomic dysregulation	Bradycardia	Sometimes	No	Sometimes
	Gastrointestinal dysmotility	Yes	No	Yes
	Thermal dysregulation	Yes	Yes	Yes
	Cold extremities	Yes	No	
	Increased sweating	Yes	No	Yes
	Ophthalmologic abnormalities	Yes	Yes	Yes
	Altered pain perception	Yes	Yes	Yes
Behavioral disorders		Sometimes	Yes	Sometimes
Neurologic abnormalities	Seizures	Sometimes	Sometimes	Sometimes
	Sleep abnormalities	No	Yes	Sometimes
Neural crest tumors		Yes	No	Yes
Decreased fetal movement		No	Yes	No
Neonatal hypotonia		No	Yes	No
Delayed motor skills		No	Yes	Yes
Delayed cognitive development		Sometimes	Yes	Yes
Dysmorphic facial features		Sometimes	Yes	Sometimes
Small hands and feet		No	Yes	No
Scoliosis		Sometimes	Yes	No
Genetic testing		No candidate genes	Parent-specific DNA methylation	*PHOX2B* gene mutation

Note: Data from these studies.[6,40–42]

Abbreviations: CCHS, congenital central hypoventilation syndrome; DNA, deoxyribonucleic acid; PHOX2B, paired-like homeobox protein 2B; PWS, Prader–Willi syndrome.

hypothalamic dysfunction and central hypoventilation are the clinical markers of the disease.

- The etiology of ROHHAD syndrome is still obscure, although genetic, epigenetic and immune-modulated etiopathogenetic theories were formulated.
- As there are not specific laboratory findings, the diagnosis is only supported by clinical criteria and the exclusion of CCHS based on the absence of *PHOX2B* gene mutation.
- Therapeutic options addressed to each clinical disturbance are supportive and involve a multidisciplinary team. Careful monitoring of these children is essential to limit morbidity and mortality associated with ROHHAD syndrome.

Table 4 Therapeutic Options in ROHHAD Syndrome

Clinical Manifestations		Treatment
Obesity		Diet Exercise
Hypothalamic dysfunction		Specific hormone replacement
Hypoventilation		Artificial ventilation during sleep or continuous ventilatory support • mask ventilation • continuous positive airway pressure • mechanical ventilation • tracheostomy
Autonomic dysregulation	Cardiovascular	Antihypertensive medication Cardiac pacemaker
	Gastrointestinal	Stool softeners Antidiarrhea drugs
	Neuropsychological	Antiepileptics Antipsychotics
	Thermal dysregulation	Regulation of ambient temperature
Neural crest tumors		Surgical removal Multimodal treatment
Metabolic disorders		Antidiabetic drugs Hypolipemiant drugs

Note: Data from these studies.[4,5]

Disclosure

The authors report no conflicts of interest in this work.

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Electronic Cigarette Use and Its Relationship with Smoking and Alcohol and Illicit Drug Consumption among Romanian University Students

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Abstract: *Background and objectives:* This study assesses electronic cigarette (e-cigarette) use and its relationship with smoking and alcohol and illicit drug consumption among Romanian university students. *Materials and methods:* A cross sectional study using anonymous questionnaire was performed in 2017 among 400 university students from Cluj-Napoca, Romania. *Results*: 95.5% of the participants had heard about e-cigarettes and 43.7% of these had tried e-cigarettes during their lifetime, while 8.9% declared using cigarettes in the previous month (one out of five students who had tried them during their lifetime). Half of the students had smoked during their lifetime and one third had smoked in the previous month. Eighty-five percent of participants had experimented alcohol intoxication during their lifetime and 45% had done so in the previous month, while illicit drug use during their lifetime and the previous month was 34% and 9.5%, respectively. The results of the linear regression analyses show a positive correlation between e-cigarette use, smoking, experimentation with alcohol intoxication, and the use of illicit drugs. *Conclusions*: Future studies as well as educational activities should address the complex relationship between e-cigarette and other substance use among Romanian youth.

Keywords: e-cigarettes; youth; health risk behaviors; Romania

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1. Introduction

The use of electronic cigarettes (e-cigarettes) among youth has grown exponentially in the past few years in several countries, their popularity being attributed to a variety of factors such as successful marketing targeting youth and the attraction derived from their novelty, product design, and flavor availability [1–7].

Their use might lead to several health problems such as acute toxicity, asthma, adverse brain development, adverse fetal development, lung cancer, and injuries related to e-cigarette battery explosions [4,8,9]. Moreover, even though they are promoted as aids for quitting smoking, several studies show that such advantages are less relevant to youth, while young people using e-cigarettes are more likely to later initiate combustible cigarette use or to continue dual use of both traditional and electronic cigarettes, which promotes the development and continuation of nicotine dependence. This raises new public health concerns about the health implications of this behavior, especially that children and adolescents increasingly take up the use of e-cigarettes in some countries [8–13].

The World Health Organization underlines that both tobacco products and e-cigarettes pose risks to health, and the safest approach is not to consume either [13]. The Forum of International Respiratory Societies recommends greater research on the health effects of electronic cigarettes and surveillance of use across different countries [14].

Several studies from all over the world, including Romania, have proved that cigarette smoking is associated with several risk behaviors such as alcohol abuse and illicit drug use among different groups of young people, while the synergistic effects and augmented risks associated with concurrent use of nicotine and alcohol or other illicit drugs have been well established [15,16]. Recently, some studies, especially from North America, have focused on the relationships between e-cigarette use and risk behaviors, but few studies have been performed in Europe, and no data are available from Romania [3,17–23]. Further, little is known about how the intention to use e-cigarettes in the future is related to alcohol and illicit drug use patterns [18].

This study focuses on Romanian university studies from Cluj-Napoca, a big university city situated in the northwest part of Romania. It has three objectives. The first one is to assess attitudes and sources of information as well as behaviors and intentions related to e-cigarettes among Romanian university students. Second, the study aims to identify the relationship and co-occurrence of e-cigarette use and smoking and alcohol and illicit drug consumption. Third, the study assesses the relationship between intention to use e-cigarettes in the future and patterns regarding consumption of e-cigarettes, traditional cigarettes, alcohol, and illicit drugs.

2. Materials and Methods

2.1. Study Sample and Procedure for Data Collection

A cross sectional study was performed in April–May 2017 among 400 university students from the four main universities from Cluj-Napoca, a big university city situated in northwest Romania. It used an anonymous questionnaire that investigated several issues related to the lifestyles of students.

A convenience sample of students was randomly chosen from eight dorms belonging to the four main universities of the town. This approach was used in order to have access to students from different faculties from the four universities, while contact of those students during their activities in the universities had several logistical constraints. Each university has its own dorms (the majority of dorms are only for female or male students and, if there are mixed dorms, they have separated parts for each gender group) with rooms where 2–4 students share the same room, but no information was available regarding the total number of students from each dorm.

A convenience sample of 100 students (50 female and 50 male) living in the selected dorms were randomly chosen from each university. The selection of students was made by randomly choosing 20–25 different rooms from each dorm and asking the students living in those rooms at the time the study was performed to fill in the anonymous questionnaire. Besides gender selection, there was no pattern in the distribution of students from different faculties and years of study from the same university in shared rooms, hence one room might be shared by students from the same faculty, but with different years of study, or from different faculties belonging to the same university. The rooms where the study was performed were chosen completely randomly because no information regarding the faculty/age of participant was available, in order to help the sampling procedure.

Students were contacted directly in the dorms by a member of the research team and were informed about the voluntary participation and characteristics of the study. The refusal rate was below 6%, and the students who refused to participate were replaced with students from the same university, living in the same dorm. The participating students filled in the questionnaires, which were collected by members of the research team from each room approximately 1 h after their distribution.

The study is part of a research project that received the ethical approval (code: 120/6.03.2015; date: 6 March 2015) of the Ethic board of University of Medicine and Pharmacy from Cluj-Napoca, Romania.

2.2. Instrument for Data Collection

The study used an anonymous questionnaire developed for this study based on data from the literature and on previous questionnaires developed and tested in several studies from Romania [2,15,16,24]. It included several sections investigating health risk behaviors among participating students.

The present study includes information collected through the anonymous questionnaires with regard to the following issues:

- Socio-demographic characteristics (age, gender, and university);
- Opinions regarding e-cigarette use (several statements were listed and students had to declare if they agreed or not with them; possibilities for answers varying from I totally agree to I totally disagree);
- Sources of information about e-cigarette use;
- Reasons for using e-cigarettes at least once during their lifetime among those who had done so;
- Behavior related to e-cigarette use (students were asked if they had used e-cigarettes at least once during their lifetime or in the previous month);
- Intention to use e-cigarettes in the next year (students were asked if they intended to use e-cigarettes in the next year; possibilities for answers varying from definitely no to definitely yes);
- Behaviors related to smoking (students were asked if they had smoked traditional cigarettes at least once during their lifetime or in the previous month);
- Experiencing alcohol intoxication (experiencing alcohol intoxication during their lifetime or in the previous month);
- Illicit drug use (students were asked if they had used any illicit drugs during their lifetime or in the previous month).

The field of research regarding e-cigarette use has only emerged in the last few years, and no standardized questionnaire is available, with several international studies trying to assess both behavior as well as knowledge, attitudes, reasons related to trying/continuing e-cigarette use, or intention to use them in the future [17–23]. The assessment of smoking, illicit drug use, and experimentation with alcohol intoxication as the presence/absence of the behavior during their lifetime or in the previous month is frequently used in research studies focusing on these topics; lifetime use showing experimentation, and previous month consumption being an indicator of current use [25,26].

2.3. Data Analyses

Opinions, behaviors, and intention related to the use of e-cigarettes, as well as smoking, alcohol, and illicit drug use were investigated for the whole sample as well as for two distinct categories of participant-students who had tried e-cigarettes during their lifetime and those who had not done this; independent sample *t*-tests and chi^2 tests were used to assess differences between the two groups with regard to the investigated issues.

Co-occurrences of e-cigarette use and smoking and alcohol, and illicit drug use during their lifetime and in the previous month were assessed.

Four univariate linear regression analyses were used in order to assess the association between e-cigarette use, smoking, alcohol and illicit drug use and socio-demographic characteristics. The dependent variable in each of the linear regressions was one of the four health risk behaviors (e-cigarette use, smoking, experimentation with alcohol acute intoxication and illicit drug use were coded as 0—no use/presence during lifetime, 1—use/presence during lifetime, but not in the last month, 3—use/presence in the last month), while the independent variables were the other three health risk behaviors, age, and gender. At the same time, a univariate linear regression analyze was used to assess the association between intention to use e-cigarettes in the next year (coded as (-2)—definitely no, (-1)—probably no, 0—I do not know, 1—probably yes, 2—definitely yes) and the four health risk behaviors as well as socio-demographic characteristics.

Data analysis was performed with IBM SPSS Statistics for Windows Version 20 program. Statistical significance is reported at $p < 0.05$.

3. Results

3.1. Opinions, Sources of Information, and Behavior Related to E-Cigarettes

The results show that 95.5% of the students had heard about e-cigarettes. Out of these, 43.7% had tried e-cigarettes at least once during their lifetime and 8.9% had declared using cigarettes in the previous month (one out of five students who had tried at least once during their lifetime).

Around 45% of the students considered e-cigarette less dangerous (one third of the never users versus half of the users) and helped smokers to quit smoking (41% of the never users vs. 51% of the users). Less than one third of the students considered that cigarettes were used only by smokers (almost half of the never users did not know what to say, while almost half of the users disagreed with this), a stronger disagreement being noticed among users (see Table 1).

Table 1. Opinions, sources of information, and behavior related to e-cigarettes.

Items	Total [a] *n* = 382	No Experimentation [b] *n* = 215	Experimentation [c] *n* = 167
E-cigarettes are less dangerous than tobacco cigarettes [d]			
Totally/partially yes (%)	44	35.7	51.6
I do not know (%)	35.2	46.5	20.6
Totally/partially no (%)	20.9	17.8	24.8
Mean (SD)	0.29 (1.07)	0.21 (0.95)	0.39 (1.20)
E-cigarettes help for quitting smoking [d]			
Totally/partially yes (%)	45	41.8	51.5
I do not know (%)	27.4	36.6	15.6
Totally/partially no (%)	26.6	21.6	32.9
Mean (SD)	0.19 (1.16)	0.16 (1.01)	0.23 (1.32)
E-cigarettes are used by smokers only [d]			
Totally/partially yes (%)	30.6	32.9	27.5
I do not know (%)	37.1	46.9	24.6
Totally/partially no (%)	32.4	20.2	47.9
Mean (%)	0.03 (1.05)	0.24 (0.96) *	−0.22 (1.11)
Sources of information about e-cigarettes			
Internet (%)	47.1	37.1 **	59.9
Commercials at sale point (%)	35.5	34.7	36.5
Newspapers (%)	5.5	4.7	6.6
Friends (%)	70	65.3 **	76
Colleagues (%)	41.3	31 **	54.5
Parents (%)	6.8	6.6	7.2
Health education activities (%)	2.6	1.9	3.6
Use of e-cigarettes in the previous month	8.9	-	20.4
Reasons for using e-cigarettes at least once during lifetime			
They are less dangerous than tobacco cigarettes (%)	-	-	13.4
To reduce the number of tobacco cigarettes (%)	-	-	13.4
To quit smoking (%)	-	-	9.3
Curiosity (%)	-	-	65.9
Other friends also have tried them (%)	-	-	26.8
Intention to use e-cigarettes in the next year [e]			
Totally/partially yes (%)	10.8	2.9	21
I do not know (%)	13.8	6.2	24.6
Totally/partially no (%)	74.8	91	54.4
Mean (SD)	−1.12 (1.12)	−1.56 (0.82) *	−0.56 (1.19)
Social influences			
Friends use e-cigarettes (%)	72.8	63.7 **	84.4
Colleagues use e-cigarettes (%)	49.5	40.1 **	62.3
Parents use e-cigarettes (%)	3.9	3.7	4.2

[a] The study sample consisted of students who had heard about e-cigarettes. [b] no experimentation with e-cigarettes during lifetime. [c] experimentation with e-cigarettes during lifetime. [d] coded as (−2)—I totally disagree, (−1)—I partially disagree, (0)—I do not know, (1)—I partially agree, (2)—I totally agree. [e] coded as (−2)—definitely no, (−1)—probably no, 0—I do not know, (1)—probably yes, (2)—definitely yes. * Statistical significant differences at *t*-test between student who have experimented with e-cigarettes and those who did not. ** Statistical significant differences at chi^2 test between student who have experimented with e-cigarettes and those who did not.

The main sources of information regarding cigarettes were friends and the internet, followed by colleagues and point of commercial sale, statistical significant differences being noticed between users and never users, the first ones indicating the internet, friends, and colleagues as sources of information more frequently with regard to this issue.

As presented in Table 1, the reasons for experimentation with cigarettes were mainly curiosity (two thirds of users) followed by the fact that other friends also did so (one quarter). The fact that they are less dangerous than traditional cigarettes and the desire to reduce the number of traditional cigarettes was declared by 13% of users, while less than 10% had done so with the intention of quitting smoking. With regard to social influences, two thirds of the students declared they had friends who used cigarettes, and 40% declared they knew colleagues who did so; the percentage of friends and colleagues using them being higher among users.

3.2. Interrelationship and Co-Occurrence between E-Cigarettes Use and Smoking and Alcohol and Illicit Drug Consumption

As presented in Table 2, half of the students had smoked at least once during their lifetime and one third had smoked in the previous month. Eighty-five percent of the study sample had experimented with alcohol intoxication at least once during their lifetime and 45% had done so in the previous month. The percentage of those who had tried illicit drugs was 34%, while 9.5% had done this in the previous month. All these behaviors were statistically significantly higher among those who had tried e-cigarettes at least once during their lifetime.

Table 2. Health risk behaviors among university students.

	Total *n* = 382 [a] (%)	**No Experimentation *n* = 215 [b] (%)**	**Experimentation *n* = 167 [c] (%)**
Smoking			
Never	46.6	69.3 **	17.4
At least once during lifetime	53.4	30.7 **	82.7
In the previous month	36.6	16.7 **	62.3
Alcohol acute intoxication			
Never	16	24.8 **	4.8
At least once during lifetime	84	75.2 **	95.2
In the previous month	45.4	29 **	66.5
Illicit drug use			
Never	65.1	81.6 **	43.8
At least once during lifetime	34.9	18.4 **	56.2
In the previous month	9.5	2.9 **	18.1

[a] The study sample consisted of students who had heard about e-cigarettes. [b] no experimentation with e-cigarettes during lifetime. [c] experimentation with e-cigarettes during lifetime. ** statistical significant differences at chi^2 test between student who had experimented with e-cigarettes and those who had not.

As presented in Table 3, the results of the linear regression analyses show that there is a positive correlation between e-cigarette use, smoking, experimentation with alcohol intoxication, and the use of illicit drugs, with the strongest association being between e-cigarette use and smoking as well as between experimentation with alcohol acute intoxication and smoking. Moreover, all risky behaviors were more frequent among male students than female students, while smoking was more frequent among younger ages.

Table 4 shows that only 13% of the students declared that they had not been involved in any of the four health risk behaviors (smoking, e-cigarettes, getting drunk, illicit drug use) during their lifetime, 26% had been involved only in one behavior (most frequent being acute alcohol intoxication), 14% had been involved in two behaviors (most frequently smoking and acute alcohol intoxication), 26% had been involved in three behaviors (most frequently smoking, e-cigarette use, and getting drunk), and 20% had been involved in all of the behaviors. Among users of e-cigarettes, almost all had been involved in other risky behaviors as well, around half of them had been involved in all of the investigated risky

behaviors, and around one third had been involved, besides e-cigarette use, in smoking and getting drunk.

Table 3. Association between health risk behaviors, socio-demographic characteristics, and mental wellbeing—results of univariate linear regression analyses.

	E-Cigarette Use [1]	Smoking [1]	Alcohol Acute Intoxication [1]	Illicit Drug Use [1]	Intention to Use E-Cigarettes [2]
	Standardized β	Standardized β	Standardized β	Standardized β	Standardized β
Age	NS	−0.126 ***	NS	NS	−0.193 *
Gender [3]	−0.334 *	−0.192 *	−0.421 *	−0.322 *	−0.245 *
E-cigarette use	-	0.445 *	0.335 *	0.374 *	0.455 *
Smoking	0.445 *	-	0.461 *	0.439 *	0.457 *
Alcohol acute intoxication	0.335 *	0.461 *	-	0.350 *	0.324 *
Illicit drug use	0.374 *	0.439 *	0.350 *	-	0.198 *

[1] coded as 0—no use/presence during lifetime, 1—use/presence during lifetime, but not in the last month, 3—use/presence in the last month). [2] coded as (−2)—Definitely no, (−1)—Probably no, 0—I do not know, 1—Probably yes, 2—Definitely yes. [3] coded as 0—male, 1—female. NS—non-significant. * $p < 0.001$. ** $p < 0.01$. *** $p < 0.05$.

Table 4. Co-occurrence of health risk behaviors.

	Lifetime *n* = 368%	In the Last Month *n* = 363%
None	**13.0**	**42.9**
1 behavior	**25.8**	**26.7**
Only smoking	1.4	7.7
Only e-cigarettes use	0.5	2.5
Only acute alcohol intoxication	23.9	16.2
Only illicit drug use	0.0	0.3
2 behaviors	**14.1**	**19.2**
Smoking and e-cigarette use	0.5	0.5
Smoking and acute alcohol intoxication	7.6	17
Smoking and illicit drug use	0.0	0.3
E-cigarette use and acute alcohol intoxication	3.3	1.1
E-cigarette use and illicit drug use	0.8	0.0
Acute alcohol intoxication and illicit drug use	1.9	0.3
3 behaviors	**26.5**	**10.6**
Smoking + e-cigarette use + acute alcohol intoxication	14.7	2.7
Smoking + e-cigarette use + illicit drug use	0.3	0.8
Smoking + acute alcohol intoxication + illicit drug use	8.2	6.6
E-cigarette use + acute alcohol intoxication + illicit drug use	3.3	0.5
All behaviors	**20.6**	**0.6**

In the previous month, 43% had not been involved in any of the risky behaviors, 26% had been involved only in one behavior (more frequently, getting drunk), 18% in two behaviors (most frequently, smoking and getting drunk), 11% in three (most frequently smoking, getting drunk, and illicit drug use, followed by smoking, getting drunk, and e-cigarette use), while less than 1% had been involved in all behaviors (see Table 4).

The sample of students who had used e-cigarette in the previous month was small, but around one third had been involved only in this behavior, while one third had also been involved in smoking and getting drunk.

3.3. Intention to Use E-Cigarette in the Future and Its Relationship with Other Health Risk Behaviors

One out of ten students declared their intention to use e-cigarettes in the future. As Table 3 shows, intention to use e-cigarettes in the future was higher among male students, while younger students were more convinced that they would use e-cigarettes in the future.

At the same time, intention to use e-cigarettes was associated with e-cigarette use, as well as smoking behavior, experimentation with acute alcohol intoxication, and illicit drug use; the strongest association was noticed between intention to and e-cigarette use, as well as smoking behavior.

4. Discussion

A study performed in 2013 among university students from Cluj-Napoca Romania showed that the prevalence of use of e-cigarettes was 25.2%, while use in the previous month was 2.3% [2]. Our study, performed in 2017, shows an increase of experimentation to 44% and that use in the previous month has risen to 8.9%. A study performed in 2017–2018 among university students from five countries situated in Central and Eastern Europe (Belarus, Lithuania, Poland, Russia, and Slovakia) showed that 43.7% of the students had used an e-cigarette at least once during their lifetime [23]. The Global Adult Tobacco Survey (GATS), performed in Romania in 2018, showed that 11.3% of the general adult population had used e-cigarettes during their lifetime, and 3.4% had done so in the previous month [27].

In the present study, similar to the Romanian study from 2013 as well as to the study performed among students from the five European countries, e-cigarette use was more frequent among male students [2,23]. The gender differences vary across countries and ages, with some studies proving a similar situation, while other did not find this [1–5].

The main reasons for experimentation with e-cigarettes were curiosity and the influence of other friends, similar to the Romanian study performed in 2013 as well as to other European studies [2,22]. On the other hand, one out of ten users did so to quit smoking, while, in the study from 2013, this reason was declared by one quarter of users. The thought that e-cigarette were less dangerous and an intention to decrease the number of traditional cigarettes was declared by 13% of users, which was more than the percentages found in the study from 2013 [2].

On the other hand, less than half of the students believed that e-cigarettes were less dangerous than tobacco cigarettes and they could help with quitting smoking, while less than one third considered that they were used only by smokers, these percentages being lower than those obtained in 2013 [2]. Moreover, students who had experimented with e-cigarette use were statistically significantly convinced that they were not used only by smokers.

Friends, colleagues, and the internet were the main sources of information; students who had tried e-cigarettes declaring to a higher extent that they had looked for information from these sources. Studies from Romania and other countries also found similar results [24,25]. Moreover, users of e-cigarettes also declared a higher percentage of friend and colleagues who used e-cigarettes, confirming the influences of peer groups in influencing opinions and behaviors, similar to other studies [18,28–32].

Moreover, the study from 2013 showed that less than 5% of the students declared that they will use e-cigarettes in the next year while, in our study, 10% of the participants did so [2]. In our study, this intention was stronger among male students and younger ages.

On the other hand, 36.6% of the students from our study were smokers (had smoked in the previous month), while the results of the Global Adult Tobacco Survey (GATS), performed in Romania in 2018, showed that, among the adult general population, the percentage of smokers was 30.7% [27]. Around half of the participants declared alcohol intoxication in the previous month, while almost 10% had used illicit drugs in the previous month. Another study, performed among university students from Cluj-Napoca, showed

an increasing trend of illicit drug use from 1991 to 2011, with 2.5% of the female students and 6.2% of the male students declaring illicit drug use in the previous month in 2011 [33].

Previous studies performed specially in North America showed robust associations between e-cigarette use and substance-related risk behaviors, being evidence that e-cigarette use clusters with risk behaviors and appears to represent problem behavior, especially the dual use of e-cigarettes and traditional cigarettes [17–20]. Our study confirms the association between e-cigarette use, smoking, alcohol acute intoxication, and illicit drug use; students who experimented with e-cigarettes during their lifetime being statistically significantly more prone to smoking, experimenting with alcohol acute intoxication, and illicit drug use both during their lifetime as well as in the previous month.

Moreover, the majority of the students had been involved at least once during their lifetime in at least of one of the four investigated health risk behaviors, with 60% being involved in more than one. More than half of the students had been involved in the previous month in at least one of the health risk behaviors, and 30% had been involved in more than one health risk behavior.

Intention to use e-cigarettes in the next year was also associated with e-cigarette use, smoking, and alcohol intoxication, as well as illicit drug use. Studies from other countries also showed the association between susceptibility to use e-cigarettes and consumption of other substances [18].

The results have several implications for practice. First, the data regarding e-cigarette use and the fact that both experimentation as well as its current use have increased among Romanian university students since 2013 and are more than double in comparison with their prevalence among the Romanian adult population shows the need for addressing the issue of e-cigarette use through health education programs and regulatory interventions, with a special focus on younger ages.

Second, the prevalence of smoking among students showed by the study underlines that smoking cessation programs targeting young adults should be implemented and funded properly in Romania. The use of illicit drugs also increased in comparison with studies performed between 1999 and 2011, which is of concern and requires more efforts for its prevention and reduction. Last, but not least, the co-occurrence of several licit and illicit drug use behaviors among university students calls for a comprehensive approach including education, counseling, and support services that help students to avoid and limit licit and illicit drug use as part of university policy.

The study is subject of several limitations. First, it has a cross-sectional design and the identification of causal relationships is not possible, while the study was performed in 2017 and the opinions and practices related to the use of e-cigarettes and other licit and illicit drugs among youth might have suffered changes since then. Second, it includes a convenience limited sample of 400 students living in dorms belonging to the main universities from a big town in Romania; selecting students from dorms rather than from the general student population may lead to bias and limits the generalization of the results beyond its sample. Similar to other studies in this field, the behavior of the participants was assessed based on their self reporting [25–27,34].

5. Conclusions

This is the first study from Romania and one of the few from Europe that has investigated the relationship between e-cigarettes use and the intention to use them in the future and licit and illicit drug use. It confirms the association between e-cigarette use, smoking, alcohol acute intoxication, and illicit drug use, as well as the association between intention to use e-cigarettes in the future, e-cigarette use, smoking, and experimentation with alcohol acute intoxication and illicit drug use.

Even though the study was performed in 2017 and in the last three years, especially during the pandemic of Covid-19, several changes might have taken place with regard to e-cigarette use and consumption of different licit and illicit drugs, it still offers information regarding cigarette use among university students from Romania, a subject that has been

previously investigated only by one study, performed in 2013. Moreover, the data offered by this study could be used to compare the situation regarding e-cigarette use and smoking and alcohol and illicit drug consumption among Romanian university students before and during the pandemic, as well as after the recovery period, if future studies investigate these issues.

Future research, as well as educational activities, should address the complex relationship between e-cigarettes and other substance use among Romanian youth.

Author Contributions: L.M.L. was involved in establishing the study methodology, data collection, and analyses as well as writing the article. C.G., M.M. and M.F. participated in data analyses and interpretation as well as in writing the article. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Methodological Challenges in Research Regarding the Lifestyle of School Children

Lucia Maria LOTREAN[1], Monica POPA[2], Edna Arrilo SANTILLAN[3], Mira FLOREA[4]

Abstract

This study focuses on challenges which could be encountered during different phases of research regarding the lifestyle of children. A narrative review was formed based on data from literature as well as on the experience of the authors in research activities in the field of healthy lifestyle promotion among different groups of Romanian children. The study presents several challenges which must be taken in consideration when planning research in the field of lifestyle and health promotion among children, starting with recruitment of participants, procedure for data collection and continuing with the choose of the instruments used for data gathering. The lifestyle components which are addressed refer to smoking, nutrition related behaviour and physical activity of school children aged 6 to 15. Several examples of challenges encountered by some Romanian research studies and the way that they were addressed will be also presented. Research in the field of lifestyle of children could be a challenging, time and energy consuming process, but definitely also a rewarding one, since the results are important pillars for designing appropriate health promotion interventions.

Keywords: Romanian children; lifestyle; research; methodological challenges; health promotion.

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Introduction

The lifestyle of children refers to several behaviours such as smoking, alimentary habits and involvement in physical activity, which have important short term and long term consequences on their health and well-being. Different studies underline the importance of promoting a healthy lifestyle among children, since it is easier to form correct attitudes and habits, than to change them later (World Health Organization, 2002; Curie, 2008; Lotrean *et al*., 2009).The lifestyle behaviours established in childhood may continue also during adolescence and adulthood, affecting the development of several diseases and interfering with the correct physical, emotional and social development (Currie, 2008; Lotrean *et al*., 2010). Hence it is very important to develop appropriate programmes and measures in order to promote a healthy lifestyle among children. Nevertheless, efficient health promotion programmes and activities must be evidence based and research activities among children can play an important role in gathering and offering important information regarding several issues which must be taken in consideration when developing, implementing and evaluating healthy lifestyle promotion activities. First, research among different groups of children could assess the knowledge, attitudes and behaviours of children with respect to several components of the lifestyle, which will help the development of appropriate educational objectives and messages. Second, research studies could identify several characteristics and opinions of the target group which will guide the way of designing, delivering and evaluating the educational activities and materials. For instance, based on children opinions, needs and preferences, one educational program could be implemented at school, during extra curricula activities or using new methods of information technology. Third, it is important to perform the effect and process evaluation of the educational programs in order to understand if the program was efficient, implemented as intended and which is the feedback received from children with respect to its content. Hence, researches, where children are involved and recognised as important participants and their opinions and views are sought, are important in the field of healthy lifestyle promotion for children. Nevertheless, several studies suggest that this type of research must be performed, tacking in account and trying to solve several challenges, dilemmas and barriers which could be encountered, since there are some inherent differences about children which make them different from adults: they may have a limited and different use of vocabulary and understanding of words, relatively less experience of the world, different social competences, and may have a shorter attention span (Barker and Weller, 2003; Punch, 2002; Eirsnadottir, 2003).

This study focuses on challenges which could be encountered during different phases of research performed among children regarding their lifestyle, giving a special attention to several examples from Romania.

Methods

A narrative review was formed based on data from literature as well as on the experience of the authors in activities of research in the field of healthy lifestyle promotion among different groups of Romanian children. The study presents several challenges which must be tacking in consideration when planning research in the field of lifestyle and health promotion among children, starting with recruitment of participants, procedure for data collection and continuing with the choose of the instruments used for data collection. Several examples of challenges encountered by some Romanian research studies in the field and the way that they were addressed will be also presented. The focus of the study will be on research among school children aged 6 to 15 years old, which in the Romanian educational system means primary and secondary school children. The lifestyle components which will be discussed refers to smoking, nutrition related behaviour and physical activity.

Results

Recruitment of participants

There are several settings which allow to the research team to get the involvement of the children in research activities assessing their lifestyle, such as: (1) school settings; (2) children clubs (sport clubs, scouts clubs, holiday camps); (3) medical settings (offices of general medicine, hospitals, community health centres); (4) family.

Table 1 presents several advantages as well as challenges encountered during the process of recruiting the participants in different settings. We would like to point out two main challenges and possible ways of addressing them.

First, despite the setting where the research take place, it is widely recognised that in order to gain children's consent and involvement in research, one has to go via adult gatekeepers who are able to limit researchers' access to the children (Barker & Weller, 2003; Punch, 2002). In the case o the research performed in schools, children clubs or medical settings an institutional approval for the research should be obtained from the administration/director of that institution. It is advisable to have a written agreement, where both rights and obligation of institution representatives and the research team are clearly depicted. In order to obtain this consent, these officials must be clearly informed about the research project: objectives of research; the research team; the activities involved by the research; duration of the research; the way the target group will be involved; the benefits of participation for the participants as well as for the society; the possible risk of participation; the assurance of anonymity/confidentiality during and after

the research is done, and during the process of dissemination; the contact data of the research team, where they can be contacted if there are questions ore issues which must be clarified before, during or after the research is done; the way the institution representatives can obtain a copy of the final results (Lotrean *et al*., 2011; Gavrilovivi & Gavrilovici, 2009). An official agreement can prevent several misunderstandings, such as the impossibility of continuing the research, if at a certain moment during data collection the director of the school change and the new director have no idea about the research project and do not want to continue it. Negotiating access to children in these institutions is therefore a process requiring researchers to be prepared to address any issues that gatekeepers may raise (Barker & Weller, 2003; Punch, 2002), including a disagreement of the officials with some research questions or instruments (for instance the school administration do not agree with asking children regarding the anti-smoking policies which are in place on school property).

On the other hand, children may be contacted through their family home. Several researchers underlined that access through the home may also be a long and complex process (Barker & Weller, 2003; Punch, 2002; Mauthner, 1997). Contacting parents of each child is a time consuming process, parents may see researchers as intrusion, and do not want such a public examination of their own private space (Barker & Weller, 2003; Punch, 2002). Nevertheless, there were also researchers who preferred this way of getting to the children, since they found the process of negotiating the access in schools too complicated and with the risk of influencing the design of the research as a result of the opinions expressed by some school officials.

Second, another challenge is represented by the issues which researchers should correctly identify and address with respect to creating the children the appropriate environment which will allow them to have the time, the mood and the disponibility to participate. In schools or children clubs, the moment of performing the research should be carefully choose, in order to prevent the interference with other activities (for instance, the research could be performed in schools during some specific hours of civic education). Moreover, research conducted at school should take into account that children may feel pressure to give 'correct' answers to research questions, since they can interpret it as a school test. Hence, adult researchers need to reassure children that there are no right and wrong answers (Barker & Weller, 2003; Punch, 2002; Lotrean *et al*., 2011) and they should express freely their own ideas and opinions.

The research activities performed in medical settings may take advantage of the possibility of involving medical doctors or nurses as part of the research team and they can gather important information from the children during their medical activity. There are big chances that health care professionals have already experience in working and communicating with children and beneficiate from children

confidence. Nevertheless, the overloaded clinical activity may be an important obstacle in motivating health professionals to participate in research activity.

Performing research with children at their home, in their own spaces can enable them to feel more comfortable. Yet adults should not assume that children necessarily prefer their own environment, they may actually prefer an adult researcher not to invade their child space or they could be intimidated by the presence of their parents (Barker & Weller, 2003; Punch, 2002). As several researchers also showed, ultimately it depends on the skills of the adult researcher to develop rapport and build up a relationship of trust both with children and the adult gatekeepers, such as parents or teachers (Eirsnadottir, 2003; Barker & Weller, 2003).

Procedure for data collection

The procedure for data collection must allow to children voluntary participation and must assure them anonymity or confidentiality.

- *Voluntary participation.* Children participating in the research activities must be assured that they could refuse to participate, without any consequences. In the case of using the questionnaire they can refuse by leaving the questionnaire blank. In the case of interviews they can refuse to answer the questions. This must be clearly explicit to them orally, but can be written also on the first page of the questionnaire (Lotrean *et al*, 2011).
- *Anonymity or confidentiality*. Whenever it is possible, the best option is to assure anonymity for the answers/information offered by participating children. For instance, in the case of using questionnaire for assessing several beliefs or behaviours of children, they will not write their names and identification data on the questionnaire. This will allow them to answer freely to questions regarding their smoking status or other health risk behaviours, without to be afraid that the teachers or the parents will find about this. Nevertheless, there are situation when the objectives of the research cannot allow for anonymity of the answers. For instance, if a study investigates the evolution during a period of time of several components of the lifestyle among children researchers perform the study two or more times and they need to follow the evolution between assessments of health behaviours of each person. In this case the only possibility is to assure confidentiality (Lotrean *et al*, 2011). Participating students must be assured that the data provided by them are confidential and only the research team will have access to them. There are studies which underline that this confidentiality should be broken only in cases where the researchers get information regarding child abuse or situations which put a serious treat to the children (Eirsnadottir, 2003; Barker & Weller, 2003). For instance,

studies assessing the lifestyle of Romanian children performed at school used several means in order to assure children that they can trust the research team, which will create the confidentiality of their answers (Lotrean *et al*, 2012a, Lotrean *et al*., 2009): (1) school teachers or administration were not involved in the process of data collection; teachers were not present in the class when the questionnaires were administered or they were present, but they stay in front of the class and did not participate in questionnaire collection; (2) school students did not write their name on questionnaires, but put their questionnaire in an envelope and wrote their name on envelope. Another possibility is that the research team allocates a code to the students and they will write their code on the questionnaire, not the name.

Table 1. *Settings for recruitment of the study sample*

	Advantages	Challenges
School settings	1. Facilitate access to many children, since a big percentage of children aged 6-15 goes frequently to school, the school drop out rates at this age in Romania being low 2. Allows the possibility of researchers to observe several components of the lifestyle of children during school activity, such as involvement in physical activity during breaks and hours for sport education, food offered in school cafeteria, smoking behaviour of children on school property 3. There are chances to receive more focus of the children, since they are used to perform several activities during school time 4. There are possibilities to involve some children in activities of data gathering by using photo cameras	1. Informed consent from school administration/ principal should be obtained 2. Often school administrations have different issues and priorities that need to be addressed and sometimes they could have a different agenda than the research team, including the risk that they do not agree with some of the research questions or instruments 3. It is advisable to obtain also the informed consent from parents, even if sometime could be a challenge to meet them. Some possibilities are to try to reach them during parents meeting convoked by teachers at school or sending them letters through children. 3. The school environment is a place for children to learn but is organised and controlled by adult teachers. Research conducted at school should take into account that children may feel pressure to give 'correct' answers to research questions (Barker and Weller, 2003) 4. Longitudinal studies can be carried out only for the period of time when children are still in the same school 5. Lack of time, since children are involved in several school activities

	Advantages	Challenges
Children clubs	1. It can access some specific groups of children which might be of particular interest for a specific research (for instance a research focused on the lifestyle of children which participate to different sport clubs) 2.Some children could feel more relaxed and talk more freely than in a school environment 3.There are possibilities to involve some children in activities of data gathering by using photo cameras	1.Informed consent from the institution representatives should be obtained 2.Informed consent from parents is needed 3.Lack of time, since children are involved in other activities
Medical settings	1.The possibility of getting information about the child also from the parents 2.The possibility of getting the medical doctors or the health care professionals as part of the research team, since they could have experience of building rapports and communication with children and, at the same time, they could get several information from their children patients during their medical activity, without to be interpreted as a interference by children or parents 3.The possibility of getting access to specific children groups, such as children with chronic diseases	1.Informed consent from the hospital director is needed 2.Informed consent from parents is needed 3.Challenges in convincing the health care professionals to be part of the research team due to overloading with clinical activity
Family	1.No need of institutional approval 2.Some children may feel more relaxed and talk more freely than in a school environment 3.The possibility of getting information about the child also from the parents 4.There possibilities of conducting longitudinal studies	1.Some parents do not want a researcher to interfere with their home privacy 2.Some children may be intimidated by the presence of their parents 3.Lack of time from both children and/or parents to participate in the research activities

Research instruments

In order to gather information from children with respect to their lifestyle there are several instruments which can be used: (1) questionnaires ; (2) interviews ; (3) focus-groups ; (4) diaries ; (5) observation ; (6) different measurements.

1. *Questionnaires* can be used for secondary school children, while having a very limited utilization for primary school children. Validity and reliability of questionnaires is always an important issue and the challenge of developing questionnaires for assessing lifestyle of children with good validity and reliability

is even higher. In order to investigate the involvement of children in one health risk behaviour, several questions must be used, in order to capture the correct answer. For instance, a research study performed among Romanian secondary school children assessed smoking behaviour by a combination of five questions (Lotrean *et al*., 2012a). First, students were asked to choose a statement that best described their smoking behaviour (e.g. 'I smoke less than weekly'; 'I smoke at least once a week'). The responses were cross-validated using an algorithm of concepts measuring current smoking (smoking in the last month, the last week and the last 24 hours) and lifetime smoking (number of cigarettes smoked during lifetime). The assessment of alimentary habits of children could be performed by using a food frequency questionnaire, which has three main parts: a list with aliments, a part where children choose the frequency of eating the specified food products during a certain period of the (for instance in the last month) and a third part which investigates the quantity of food eaten with each occasion. In order to make children to better estimate the quantity, a definition of what a portion is should be clearly formulated and children can decide how many portions they have eaten. In a study regarding alimentary habits of Romanian secondary school children vegetables intake, respectively fruit intake were assessed by two items each (Lotrean *et al*., 2012b). The first item was a food frequency question: How often did you eat fruits/vegetables in the last 7 days? The second item referred to the number of portions of fruits, respectively vegetables they consumed on such days. A clear definition of one portion was included in the questionnaire for both vegetables and fruits. Similar with other studies (World Health Organization, 2002; Mullarkey *et al*., 2007), one portion of fruits was defined as a whole fruit (e.g. medium apple), three-fourths cup (178 mL) fruit juice, or one-half cup (120 mL) cut-up fruit. For vegetables, a serving was defined as 1 cup (240 mL) raw leafy vegetables (e.g, lettuce), one-half cup other vegetables, or three-fourths cup vegetable juice. Other possibilities of making children to better understand what a portion means are represented by showing to children pictures with one portion of the specific food. Different studies also underline the importance of explaining to the children very well all these issues connected to estimation of food quantity and frequency of consumption, since it could be difficult for some of them to make correct estimation (Mullarkey *et al*., 2007).

2. *Interviews*. This type of instruments can be used both for primary school children and secondary school students. Some researchers suggest that some children prefer to be interviewed together with another child colleague or that some little children could cooperate better if during the interviewing process they are allowed to play or draw something (Eirsnadottir, 2003). Moreover, the clarity of language and the experience of the researchers in communicating and building connection with children are vital. Sometimes children are not used to expressing their views freely or being taken seriously by adults because of their position in adult dominated society. The challenge is how best to enable children to express

their views to an adult researcher and how to 'maximise children's ability to express themselves (Barker & Weller, 2003).

3. *Focus groups*. They could be utilised in order to gain deeper insight regarding the opinions of older children from secondary schools on a specific issue. Some children can be stimulated to talk during focus groups activities, while others may lack confidence in communicating directly in the presence of other peers.

4. *Diaries*. Diaries where there are written the food products and/or the type of physical activity from a certain period of time (generally 3-5 days) can offer valuable detailed information about the lifestyle of the investigated person, but they have limited utilization in research among children. This type of instruments can be used only with older children, with a high literacy and good motivation in performing such a task.

5. *Observations*. Adults researchers can perform several observation in different settings in order to investigate how children behave with respect to different lifestyle components (for instance the smoking behaviour of children on school property), but it offers some qualitative data which generally should be completed with data gathered using other types of instruments.

6. *Measurements*. Several types of measurements could be used in order to validate the information offered by children. For instance biochemical determinations of plasma and salivary cotinine and thiocyanate or expired air carbon monoxide could be used to validate smoking behaviour declared by children. Several studies, however, have found high correlations between self-reports and biochemical assessments of children smoking behaviour when confidentiality of responses is assured (Dolcini *et al*., 1996). Another example refers to the use of a pedometer- a device, usually portable that counts each step a person takes by detecting the motion of the person's hips. In order to better asses the involvement of children in physical activities, researchers could ask them to wear pedometers for several days.

Conclusions

Research in the field of lifestyle promotion among children need to be carefully planed. The setting where the research is performed and the instruments for data collection must be chosen according with the age and socio-educational characteristics of the children, the study objectives and the possibility of receiving access to children from the parents/persons responsible with the education and well being of the children. The concentration span, the life experience and social competencies, the communication ability of children are important factors which influence their capacity of expressing freely their opinions and ideas and raise challenges to adult researchers. Nevertheless, identification of these challenges

and seeking for appropriate solution to overcome them have the potential to offer valuable results which increase the chance of understanding the lifestyle related behaviours of children, the factors which influence them and the type of educational activities which should be developed for children. Hence, research in the field of lifestyle of children could be a challenging, time and energy consuming process, but definitely also a rewarding one, since the results are important pillars for designing appropriate health promotion interventions.

Acknowledgement

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ORIGINAL RESEARCH

Lights and Shadows of the Perception of the Use of Telemedicine by Romanian Family Doctors During the COVID-19 Pandemic

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Introduction: Telemedicine has emerged as a critical technology to mitigate SARS-CoV-2 infection. We aim in this work to explore how general practitioners (GPs) perceived the use of telemedicine, recently recognized and reimbursed by the Public Health Insurance House (PHIH) for primary care (PC) provision.

Methods: A cross-sectional study was performed in 2020 in one county of Romania using an anonymous questionnaire that assessed physicians' perceptions regarding teleconsultation, reliability in tele-decision, remote pathology management, pregnant women's surveillance, patients' satisfaction with telemedicine, the need for its further reimbursement. Bivariate correlation was used to measure associations between the investigated issues.

Results: More than a quarter of GPs (28.6%) found it easier to address patients' healthcare needs remotely, while 60.7% considered time-consuming teleconsultations compared to face-to-face visits. Tele-diagnostic uncertainty was expressed by 64.3% of physicians, and a quarter were confident in tele-decisions. Almost half of GPs (43%) observed patients' satisfaction with tele-visits, while half said patients encountered difficulties using technology. A large percentage of doctors (62.5%) perceived that patients felt as well treated by virtual as in-person visit and 91.1% suggested post-pandemic reimbursement. The results of the bivariate correlation showed that physicians who perceived positive patient feedback on telemedicine were more supportive of subsequent reimbursement.

Conclusion: This study showed the GPs' positive perception of the use of telemedicine. Its adoption in PC has shed light on the shadows of the pandemic. The time-consuming nature of teleconsultations, uncertainty in tele-decisions, patients' difficulties in using technology were seen as shadows of telecare. However, most of the GPs surveyed agreed with the need for further reimbursement. Future work should focus on innovative solutions for integrating telemedicine as complementary form of PC, the need for telemedicine-based training for GPs to improve capacity building, and patients' perceptions of virtual care, helping to build trust and satisfaction.

Keywords: telemedicine, primary care, family doctor, perception, Covid-19 pandemic

Plain Language Summary

- The recognition and reimbursement of telemedicine by public health authorities during the COVID-19 pandemic in Romania brought light into the shadow of the pandemic.
- Our study describes the perception of the use of telemedicine by family doctors during the COVID-19 in lights and shadows.
- We considered as lights: the rapid adjustment of doctors to tele-decisions, their proposal to reimburse telemedicine beyond the pandemic, the positive reaction of

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patients to the critical transition from conventional to virtual consultation, almost two-thirds of them feeling as well treated by virtual as in-person visit and a quarter observing a greater availability of solving their needs through telecare.

- The shadows of the rapid transition to remote alternative care identified by our study were: longer duration of teleconsultations, uncertainty in making remote medical decisions and difficulties of some patients in using communication technology.
- Although telemedicine was initially reimbursed only during the state of emergency, its contribution to pandemic mitigation and positive perception by both healthcare providers and patients led PHIH to continue reimbursement during the COVID-19 pandemic.

Introduction

Telemedicine has been rapidly evolving over the past several decades, but it has not yet been widely implemented into the healthcare system due to regulatory laws of concern and lack of supportive payment structures.[1,2] The term telemedicine was initially used to refer to the provision of remote healthcare services using information and communications technologies (ICT). Telehealth is a term that was introduced as a result of the widespread use of telemedicine, such as medical education and health systems management. New terms like e--health, m-health and connected health have emerged, recently. E-health was designed to refer to a wide range of data processing applications, the use of the internet in health systems and health promotion applications. Telehealth and e-health can be considered as an extension of the original term telemedicine. However, the terms telemedicine, telehealth and e-health are often used interchangeably by both healthcare professionals and consumers.[3,4] Telemedicine is implemented using ICT either asynchronously or synchronously via audio and video systems.[5,6]

Prior to the Coronavirus 2019 pandemic (COVID-19), regulatory and reimbursement issues prevented the full introduction of telemedicine into the health system in many countries.[2]

Literature Review

There is a growing interest in its adoption to provide healthcare, in its potential to reduce the exposure of patients and healthcare professionals to the risk of SARS-CoV-2 infection, to preserve protective equipment, to reduce delays in caring for non-covid patients and to respond to patients' preference for virtual visits due to fear of exposure to infection.

Telecare emerged as an effective solution for prevention and treatment of new coronavirus infection, contributing positively to the safe provision of primary care (PC) during the pandemic. Since 2005, the World Health Organization (WHO) established a global observatory for e-health to monitor the development of ICT for health care, including telemedicine, and to provide reliable guidance on best practices and standards.[7] It has progressed far less in lower-income countries than in high-income countries both in terms of the number of countries with established services and the proportion of telemedicine services offered. In April 2020, the WHO mentioned telemedicine among its key services in "strengthening the response of health systems to the COVID-19 pandemic".[8]

The current pandemic prompted outpatient medical centers to change their health delivery system, to include tele-visits supporting the continuity of care. Telemedicine should be seen not only as a temporary emergency alternative, but as a convenient, safe, scalable and effective way to provide healthcare and increase access to quality care.[9] In addition to virtual visits, text applications, e-mail and mobile telephony, telemedicine facilitates the exchange of information not only between patients and doctors, but also interprofessional communication between family doctors and specialists.[5]

Over the past several years, researchers have been exploring the advantages and disadvantages of telemedicine compared with face-to-face consultation. The advantages of telemedicine: cost-effectiveness, increased access to specialized services, its potential to help mitigate SARS- CoV-2 infection and alleviate the current or emerging physicians shortage in many countries are well highlighted by this pandemic.

Disadvantages include lack of available technological resources in low-income and some middle-income countries, issues with patient data security, physicians' uncertainty in tele-decisions because of the challenges in conducting patient examination.[1] While telemedicine is gradually delivered through smart devices, the technology usually requires both the patient and physician to learn how to use these platforms.

Training is needed to help physicians provide remote healthcare, which requires knowledge and upskilling to be able to use virtual technology and equipment. Moreover, patients need to be educated so that they can be aware of virtual healthcare solutions and their benefits. Telemedicine

could be publicized through social networks to create awareness, as elderly people may have difficulty using ICT.[10]

There are countries where policy changes have focused on improving reimbursement models and the development of digital infrastructure, thus facilitating the acceleration of telemedicine adoption.[11]

Lack of official recognition of teleconsultation before the Covid-19 pandemic in Romania, a member country of the European Union, with high internet speed, but which failed to finance them, although they were provided for years by general practitioners (GPs), especially in rural areas, justifies the need to research how they perceived the adoption of telemedicine during this crisis and how they see the improvement of future health policy.

When the state of emergency was decided at the national level, the public health authorities (PHA) encouraged family doctors to provide healthcare services remotely, as one of the measures taken to increase social distancing and home confinement. Moreover, in response to the needs of the pandemic and the WHO recommendations of April 2020, that "other countries will make their decision in the coming weeks to include telemedicine as a Standard Operating Procedure (SOP) for the prevention and treatment of COVID-19",[12] the executive decided for the first time in Romania by Government Decision 252/30 March 2020, the reimbursement of teleconsultations in PC starting with March 30, 2020.

During the state of emergency, and then in the alert status, GPs provided remote consultations, which could be performed by any means of communication, with a maximum of 8 consultations/hour. Patients received teleconsultations for any symptoms suggestive of coronavirus infection and other pathologies, even if they did not have public health insurance and were informed about the limits of tele-visit and the need to call the GP's office or the emergencies department if symptoms worsen.

There are fewer studies focused on the adoption of telemedicine to support provision of PC. Considering the importance that changes are made to adopt and finance telemedicine services during the pandemic into the Romanian healthcare, a research on GPs' perception of the critical transition to virtual visits and how they saw patients' satisfaction with this approach is justified. As the pandemic continues and evolves, physicians' opinion on the future of telemedicine and how they expect this technology to be implemented after the COVID-19 pandemic are of interest.

We aim in this work to explore how family physicians perceived the use of telemedicine, recently recognized as a tool for PC provision and reimbursed for the first time by the Romanian Public Health Insurance House (PHIH). In addition, we analyzed their opinions on the need for its further reimbursement and patients' satisfaction using ICT as perceived by family doctors.

Materials and Methods

Procedure for Data Collection

In this cross-sectional study, we developed an anonymous questionnaire and distributed it online between April and September 2020 to 108 family doctors in Cluj County, a mountainous region in northwestern Romania, with many isolated rural areas, with 737,992 inhabitants. Cluj-Napoca is the third city in Romania, being one of the most important academic centers, with 308,000 citizens.

The questionnaire aimed to assess family physicians' views on telemedicine as PC service tool adopted during the emergency state of the Covid-19 pandemic. It was administered online as a Google form in Romanian language and took approximately 13 minutes to complete.

The studied population targeted for this online survey was represented by GPs who practiced in PC offices in Cluj County. The invitation to participate was sent to family doctors from a mailing list established over several years of collaborative projects between the Department of Family Medicine at the University of Medicine and Pharmacy and The Society of Family Doctors from Cluj. The objectives and characteristics of the study were clearly explained, and participation was voluntary by accessing the link. By filling in the questionnaire, the participants agreed to participate; physicians who refused to participate did not complete the questionnaire. The response rate of family doctors during the demanding COVID-19 pandemic, including the state of emergency and part of the alert period was 51%.

Instrument for Data Collection

The questions of the designed questionnaire were grouped into sections and coded as follows.

Perception of Teleconsultations and Reliability in Remote Decision Making

Participants were asked to rate the teleconsultation compared to in-person visit, possibilities of answers being: "more difficult and time consuming" (coded as −1), "the

same" (coded as 0), "easier" (coded as 1). Another question investigated their confidence in making decisions remotely, with possible answers: "the correct establishment of the diagnosis and treatment may be affected" (−1),

"I did not notice significant differences" (0), "I consider that telemedicine does not affect the correct establishment of the diagnosis and treatment" (1).

- *Perception of the management of acute and chronic pathology and surveillance of pregnant women in primary care during the pandemic*

Participants were asked how they perceived the remote management of acute pathology, possibilities of answers being: "I noticed that solving the problem became difficult" (−1), "we could only partially solve the problem" (0) and "as before" (1). Asked how they perceived the chronic pathology management in crisis, the possibilities of answer were: "inadequate, as many sections were intended for COVID-19 patients only" (−1), "were resolved late, by planning to a specialist" (0), "as before" (1)

The question focused on opinion regarding how has been affected the surveillance of pregnant women in PC during the pandemic, was coded: (−1) for "patients have postponed in-person visits in GPs' office",

(0) for "the frequency of checks at the office during the pandemic did not change", (1) for "patients presented to the GPs' office more often than before, preferring in-person consultation.

- *Patients' satisfaction with the use of communication technology to address their health care needs in primary care, as perceived by family physicians.*

This section has 2 questions about how GPs have noticed that their patients have reacted to telemedicine in terms of technology, respectively the quality of medical services provided, with 3 possibilities to answer: negative reaction (−1), indifference (0) and positive reaction (1). Moreover, they were asked how they think the patients perceived tele-visits, with 3 possible answers: "the patient felt neglected" (−1), "felt equally well treated" (0), "felt better and more promptly treated" (1).

- *Opinion of family doctors on the need for further reimbursement of telemedicine by the Public Health Insurance House (PHIH) after the pandemic*

The last question on the need to keep teleconsultation as a complementary service and its reimbursement after the pandemic was coded as follows: (−1) for "no, because I do not consider that a teleconsultation has the same accuracy as a classic consultation", (0) for "I do not care" and (1) for "yes, it should be preserved and further reimbursed" (1).

Data Analyses

The prevalence of the investigated issues was calculated. Three scales were created regarding *the perception of teleconsultations and the reliability of remote decision-making* (Cronbach's alpha = 0.57), *the perception of acute and chronic pathology management and the supervision of pregnant women in PC during the pandemic* (Cronbach's alpha = 0.62) and *patient satisfaction with the use of communication technology to meet their health care needs in PC, as perceived by GPs* (Cronbach's alpha = 0.65). Each scale was created by summing the codes of the comprising questions for every participant.

The bivariate correlation was used to assess the correlation between the three scales and the opinion of family doctors on the need to reimburse telemedicine after the pandemic.

Statistical analyses were performed using SPSS 20 statistical program. Results with statistical significance are reported at $p < 0.05$.

Results

Opinions of Family Doctors Regarding the Use of Telemedicine

More than a quarter of GPs found it easier to address patients' healthcare needs remotely, while half responded that teleconsultations are time-consuming compared to face-to-face visits (Figure 1.).

Almost two-thirds of the family doctors expressed uncertainty about the correctness of the diagnosis established by tele-visit, and a quarter were confident in making decisions remotely (Figure 2.).

In terms of resolving acute pathology, the perception of half of the family doctors was that they solved it as before, and more than a quarter noticed that the solving became difficult, many of the acute diseases' symptoms being difficult to differentiate from those of the infection with the new coronavirus (Figure 3.).

On the other hand, chronic pathology was more difficult to resolve during this period, with almost half of GPs responding that scheduled reevaluations could not be

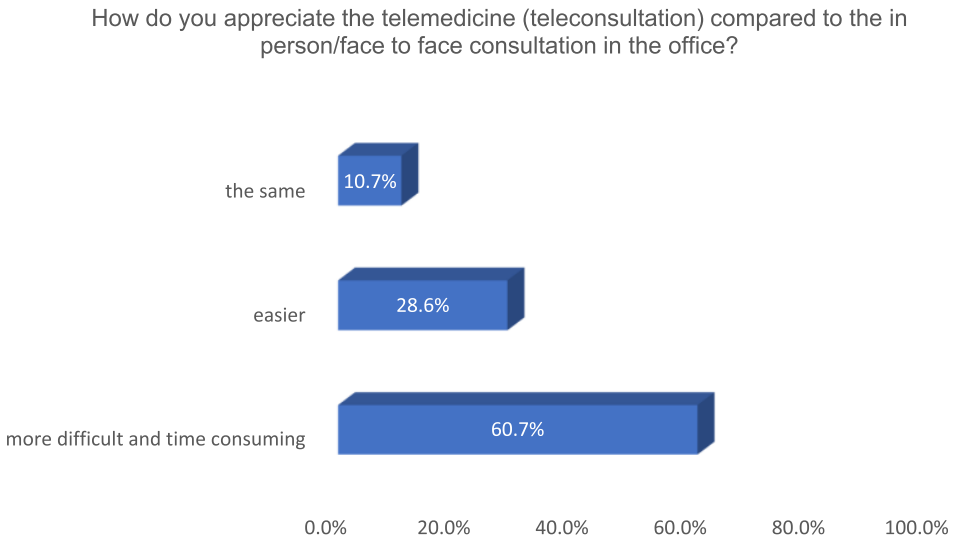

Figure 1 Perception of teleconsultations by GPs compared to in-person consultations.

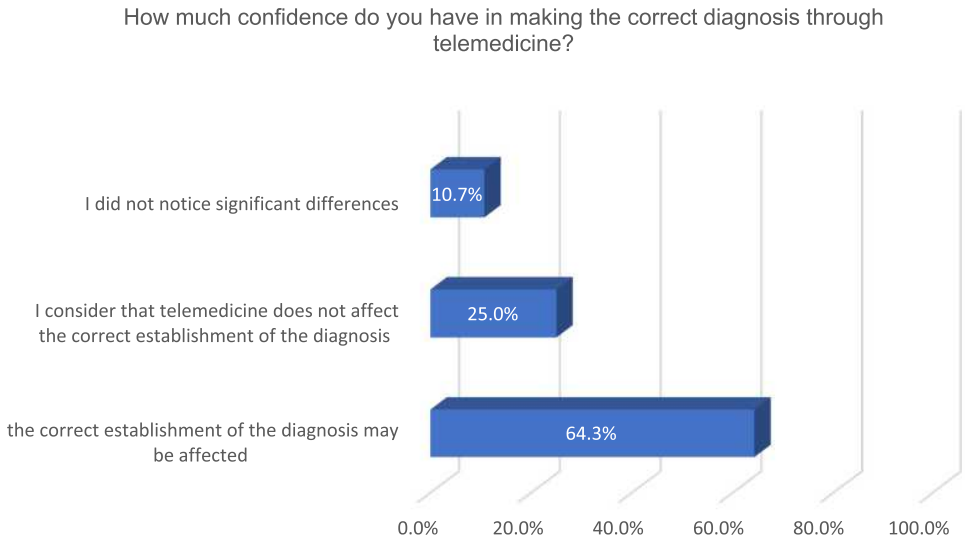

Figure 2 Family doctors' confidence in making decisions remotely.

performed because most hospitals were intended for COVID-19 infections (Figure 4.).

Supervision of pregnant women was affected by the fear of Sars-CoV-2 infection, causing delays in their presentation at scheduled visits. Most family doctors reported that their registered pregnant women preferred teleconsultations and video consultations, while a third said that the frequency of consultations in their offices for pregnancy surveillance has not changed (Figure 5.).

According to the periodic assessment of patient satisfaction by family physicians, almost half reported that their patients were satisfied with this way of interaction and the use of communication technology, which simplified the solution of their healthcare needs (telephone consultations, WhatsApp video consultations, prescription received electronically). The other half of GPs said, on the contrary, that patients encountered difficulties using communication technology with the doctors and nurses (Figure 6.).

In terms of the quality of healthcare services provided, half of family physicians noticed that for their patients the quality of virtual and in-person consultations seemed to be the same. However, a quarter of GPs considered that their patients felt insecure about the accuracy of the diagnosis in the absence of an objective examination, while another quarter appreciated that patients were equally satisfied with teleconsultation as well as in-person visit to the office (Figure 7.).

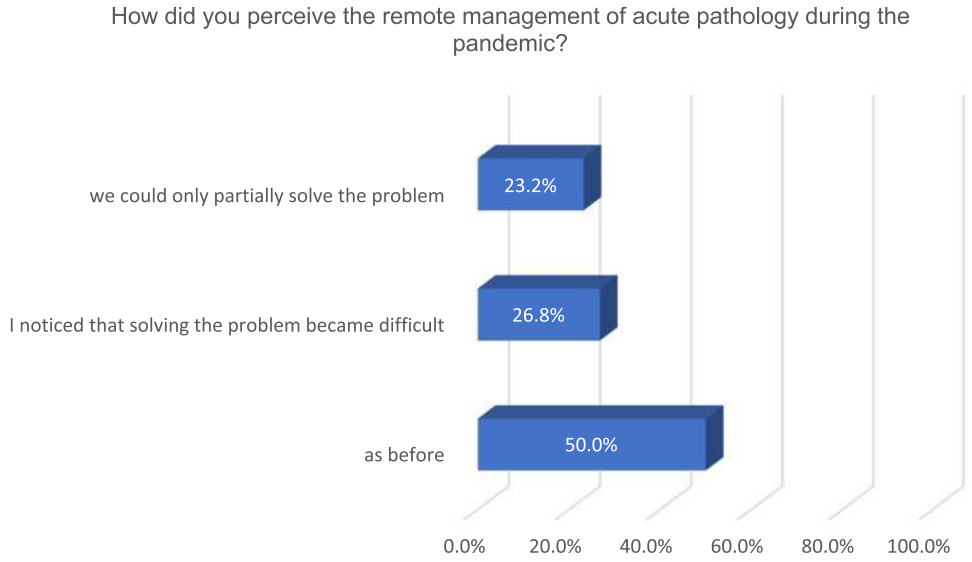

Figure 3 Perception of the remote management of acute diseases during the pandemic.

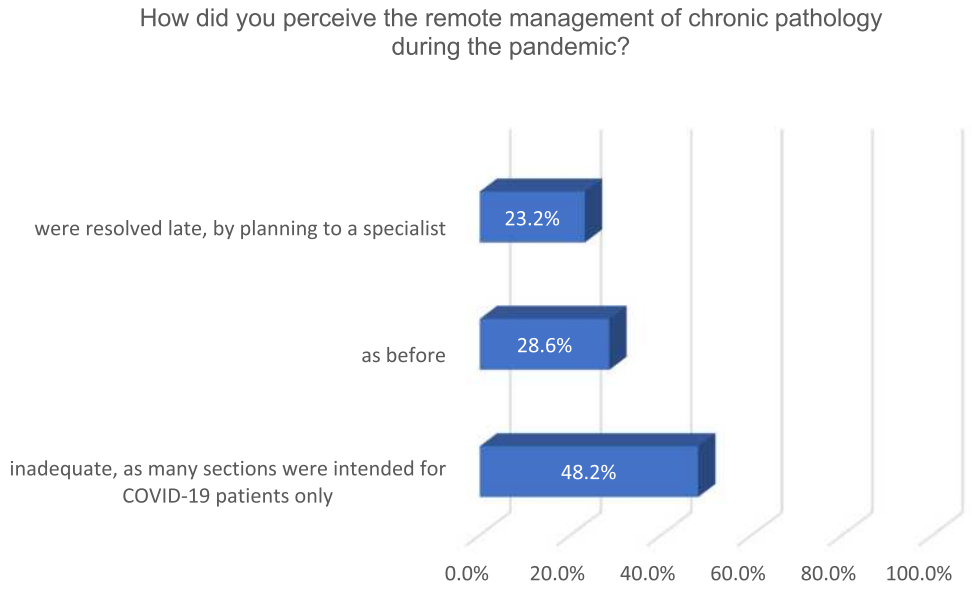

Figure 4 Perception of the remote management of chronic pathology during pandemic.

As regards the general approach of patients through telemedicine tools during the pandemic, family physicians perceived that almost two-thirds of their patients felt as well treated through virtual as in-person visit, a quarter noticed more availability to address health needs through telecare, while less than a tenth of patients experienced a feeling of being neglected (Figure 8.).

The need to continue beyond pandemic the provision of PC through telemedicine was agreed by almost all family doctors and they considered it should be reimbursed continuously as complementary PC service. Only less than a tenth of the physicians surveyed suggested that teleconsultation should not be maintained post-pandemic, given that it does not have the same accuracy as a conventional visit (Figure 9).

Associations Between Perceptions of the Use of Telemedicine During the Pandemic

As Table 1 shows, family doctors who perceived positive feedback on telemedicine from their patients were more supportive of its further reimbursement and had higher

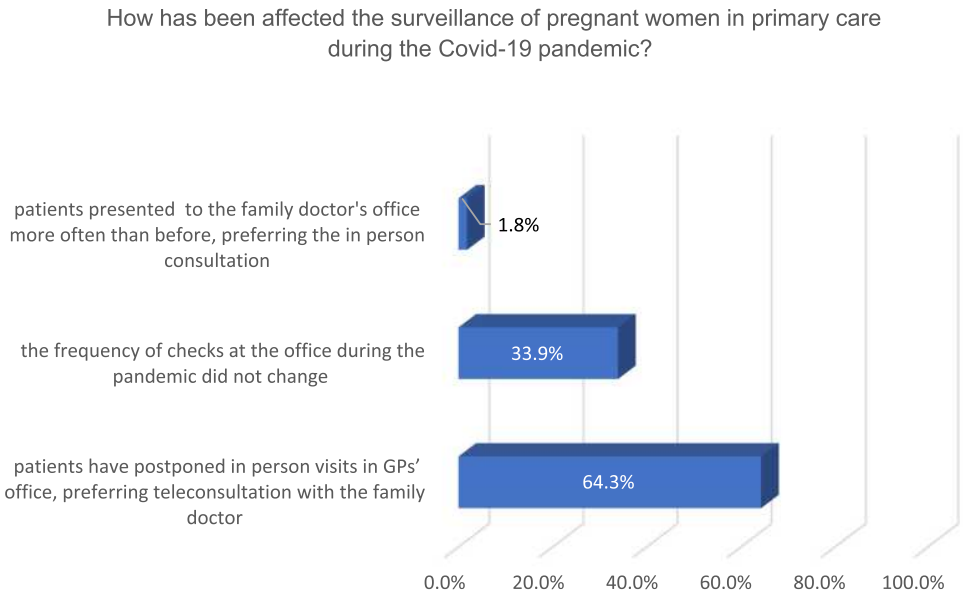

Figure 5 Pregnant women preferences for remote vs in-person consultations perceived by GPs.

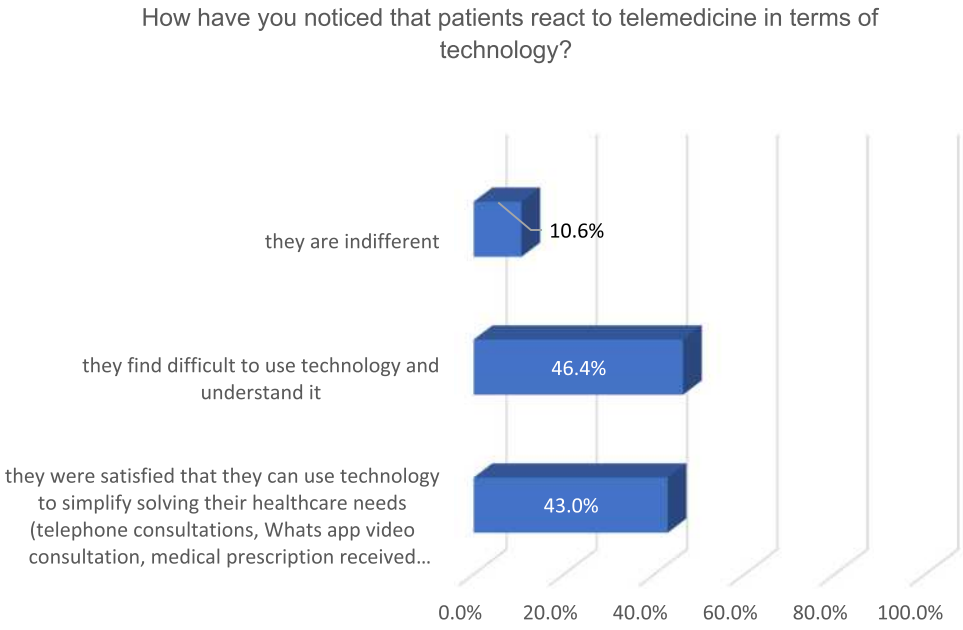

Figure 6 Patients' reaction to telemedicine regarding the use of technology, perceived by GPs.

scores on scales about perception of teleconsultations and reliability in remote decision making and perception of the management of acute and chronic pathology and surveillance of pregnant women in PC during the pandemic (Table 1).

Discussion

Covid-19 pandemic has made telehealth tech to be in the spotlight. The prompt need constrained physicians to temporarily conduct their usual offline activities by using ICT, gaining new experiences in telecare and affecting their perceptions about tele-decisions.[13] A Chinese study showed 70% growth in virtual consultation as compared to conventional visits from March 25th, 2020 until April 17th, 2020.[14]

Physicians are attracted to evidence-based technologies and digital tools that increase patient comfort and adherence, as well as improving and diversifying their clinical practice.[15]

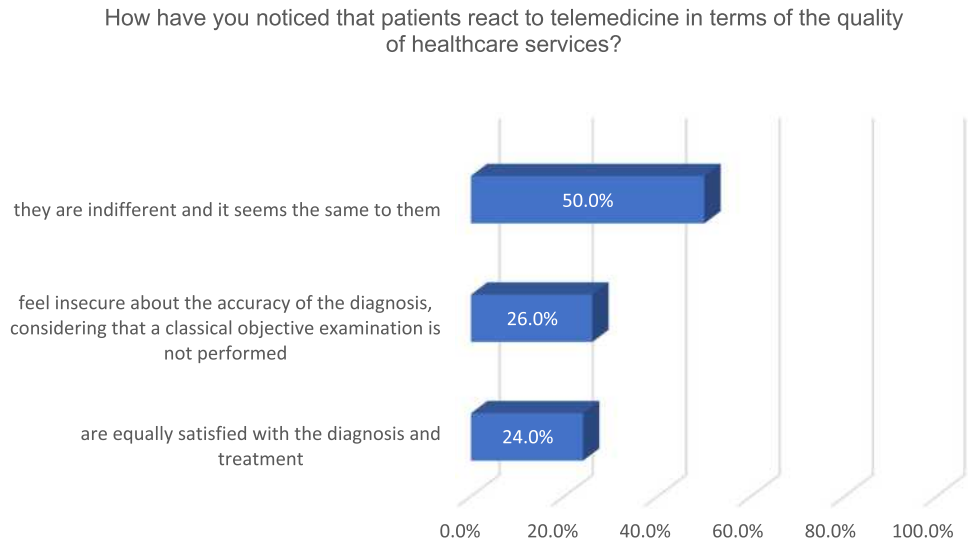

Figure 7 Patients' reaction to telemedicine regarding the quality of healthcare services provided, as perceived by GPs.

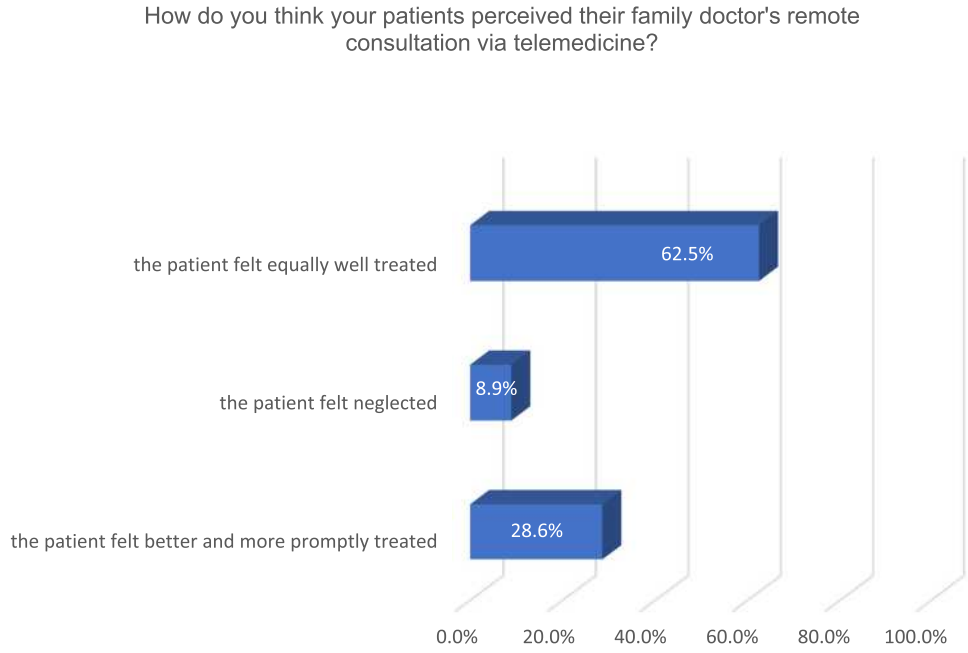

Figure 8 The general perception of telemedicine by patients according to family doctors.

Unrecognized and not reimbursed before the COVID-19 pandemic as a tool for providing PC in Romania, the adoption of teleconsultation made more than half of family physicians perceive it as more difficult and time consuming than in-person visit. Similar to the results of our study on the chronophagous nature of televisits the British GPs reported the time-consuming daily phones, emails and complex electronic medical record protocols.[16] Unexpectedly, in the United States among physicians currently using telemedicine for consultation, nearly half (48%) are using it for the first time.[17]

Telehealth services offer benefits to all people registered on the GPs' practice list, increasing access to healthcare services, child development surveillance,[18,19] remote management of the elderly with chronic comorbidities and helping to prioritize home visits.[20] Our results are consistent with other studies, revealing the positive perception of physicians and their openness to use telemedicine as an

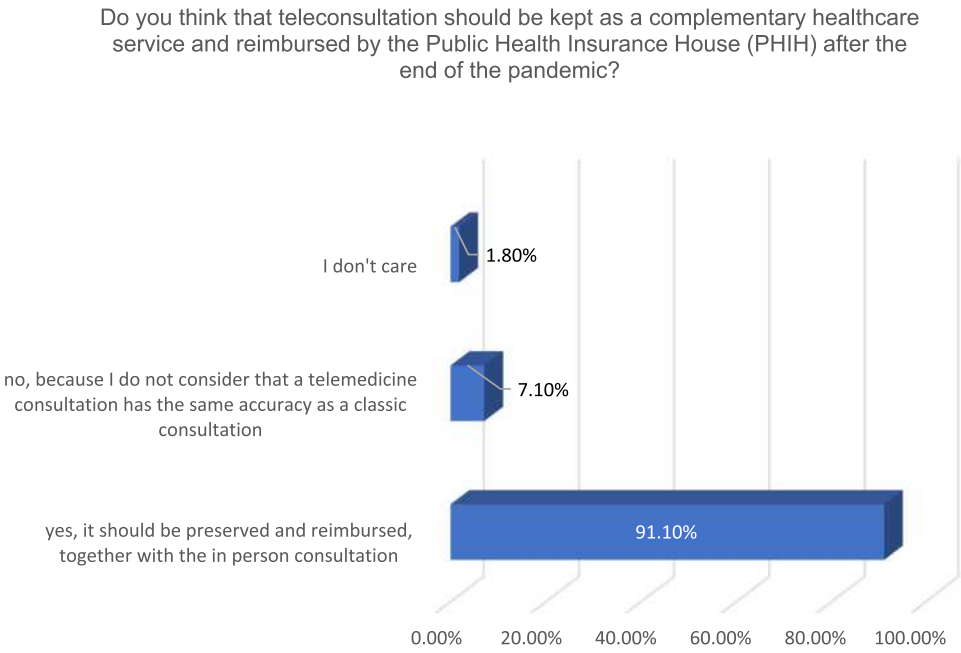

Figure 9 The need to continue post-pandemic the provision of healthcare services through telemedicine in primary care perceived by GPs.

effective way to provide healthcare services during the pandemic.[13]

In addition to the healthcare delivery, there is a considerable utilization of telehealth in medical education.[21] Some of the family doctors surveyed were involved in academic teaching, as assistant professors in the Department of Community Medicine, the discipline of Family Medicine at our university. They expanded their ICT skills and used educational platforms, having previous experience in simulating patients to train students and residents in family medicine.[22]

However, there are limitations to remote medical practice that physicians should be aware of, as the absence of physical examination findings raises uncertainty and concern.[23] According to a pre-pandemic study, tele-visits led to a correct diagnosis between 65% and 94%, while standard care protocols were followed in 34% and 66% of them.[24] In the present study, almost two-thirds of GPs (64.3%) reported uncertainty about the correctness of the diagnosis established using telemedicine and a quarter expressed confidence in making decisions remotely. Surveillance of pregnant women in PC during the COVID-19 pandemic was well supported by telemedicine, as our study showed, with most GPs reporting that registered pregnant women preferred tele-visits. These results correspond to those of another study conducted in two prenatal practices in New York City, where about one-third of the surveillance visits of pregnant women were performed by telehealth (31.8%). By the fifth week, 56.1% of family practice visits and 41.5% of clinic visits were made through telemedicine tools.[25] Nevertheless, a remote consultation is not intended and will never fully replace an in-person visit, due to the lack of objective clinical signs

Table 1 Associations Between Opinions Regarding the Use of Telemedicine

	1**	2**	3**	4**
Perception of teleconsultations and reliability in remote decision making (1)*	–	NS	0.49	NS
Perception of the management of acute and chronic pathology and surveillance of pregnant women in primary care during the pandemic (2)*	NS	–	0.33	NS
Patients' satisfaction with the use of communication technology to address their health care needs in primary care, as perceived by family physicians (3)*	0.49	0.33	–	0.43
Opinion of family doctors on the need for further reimbursement of telemedicine by the Public Health Insurance House (PHIH) after the pandemic (4)	NS	NS	0.43	NS

Notes: * The scale was created by summing the codes of the comprising questions for each participant, as explained in detail in the methodology. ** Only the Pearson correlation coefficients of the statistically significant correlations are described.
Abbreviation: NS, non-significant.

and the interpersonal transmission of non-verbal signals expressing trust and empathy.[26]

Regarding patient satisfaction with teleconsultation as perceived by half of the GPs in our study, this is consistent with other studies. A study pointed out that 95% of patients who were treated via telemedicine during the COVID-19 pandemic rated it to be useful as in-person visit.[27] Patients identified the convenience, efficiency, communication, confidentiality, and comfort of their own supportive environment as important areas to consider when evaluating virtual PC consultations versus office visits.[28] Other studies have shown that in countries where remote healthcare services were used pre-pandemic, 86% of patients were satisfied with the virtual interaction. In addition, the acceptance of teleconsultation seemed to be linked to patients' trust with their local health system and staff.[29] A survey of patients' perceptions of telehealth in the United States of America during the COVID-19 pandemic found satisfaction was high both in new and previous users of telehealth but new users were more motivated to avoid waiting rooms and potential infection.[30]

Yet, many patients have difficulties in understanding and using ICT. As our study showed, the technological literacy of patients varies, and some of them, 46.5% encountered barriers to connection through telemedicine due to lack of access to technology and insufficient social assistance. People with poor technological literacy, who lack access to the Internet, need help from volunteers and technology companies who can create low-cost plug-and-play telemedicine devices.[31]

Despite the fact that there remains an amount of skepticism and uncertainty regarding telemedicine, especially regarding the efficiency, safety and adequacy of existing regulations, there are studies that recommend and support the continuity of telehealth activities beyond the COVID-19 pandemic.[13] In our study, most family physicians (91.1%) considered necessary to continue PC provision through telemedicine post-pandemic. In Brazil, it has been signaled that the lack of regulation on the use of telemedicine was an important barrier to assist patients and 64.39% of the physicians wanted a regulation that would allow the expansion of the telehealth care services.[32] Surprisingly, another study showed that when the pandemic ends, only one-fifth of physicians using telemedicine tools expect to use them significantly more than before the pandemic.[33]

A literature review analyzing the PC provision in 6 countries suggests that COVID-19 is testing healthcare systems, even in well-resourced countries.[34] As our study has shown, government policies play a significant role in managing this difficult period of long-term COVID-19 pandemic. The decision of the Romanian government to adopt and reimburse teleconsultations during the pandemic and to continue today, has benefited patients and protected the health of medical staff.

Having yet no definitive endpoint, this pandemic requires creative solutions, such as the scale-up of telehealth, contributing to decrease its impact.[21] New telehealth solutions have emerged, improving the quality of tele-decisions.[35] The latest inventions used to combat the novel SARS-CoV-2 infection are artificially intelligent (AI)-based conversational agents, known as health chatbots. They enable patients to interact with software applications that use AI-based tools, accessed through a website or social media messaging platforms.[36–39]

Before the pandemic, a PC chatbot system was created to assist GPs by automating the patient intake process. This interactive system called Mandy is not designed as a diagnostic or clinical decision-making tool but an assistant, helping to free up the time of family doctors for more meaningful interactions with patients.[40] These technologies are multi-tasking: ask and answer questions, create health records, complete forms and generate reports.

During the pandemic, the WHO Technology program developed a chatbot to fight COVID-19, an initiative which can be accessed via WhatsApp and Facebook messenger. It is a new WHO interactive chatbot that aims to combat COVID-19 misinformation.[41] The use of health chatbots to combat COVID-19 is a practice still in its infancy. Further research will lead better understanding of this novel technology's applications and improve their functionalities and usefulness.[39]

The speed with which telehealth is progressing can have a significant effect on advancing healthcare in the future. One should view the current crisis as both a challenge and an opportunity to assess the impact of digital tools on access to care, quality of care, and the financial impact on the healthcare system.[15]

Implications for Practice

The COVID-19 pandemic continues and patients with acute and chronic conditions should be cared for safely. Telemedicine has existed for decades, but its widespread adoption in this long-term crisis has integrated it into the daily routine, increasing access to care and helping GPs to diversify the provision of PC services. As our study showed, family doctors considered that telemedicine should be implemented not only as a temporary alternative during the crisis, but beyond the pandemic. Telemedicine-based training for family

physicians can improve capacity building and streamline office management.

Implications for Health Policy

Although telemedicine was initially reimbursed only during the state of emergency and alert in Romania, its contribution to pandemic mitigation and positive perception by both patients and healthcare providers influenced health policy and led PHIH to continue its reimbursement.

Conclusion, Limitations, and Future Works

This study showed the positive perception of family doctors who quickly adapted to teleconsultations, despite concerns about decision-making remotely. The recognition and reimbursement of telemedicine for the first time by PHIH have shed light on the shadows of the pandemic. The time-consuming nature of teleconsultations, the uncertainty in tele-decisions and difficulties of some patients in using communication technology were seen as shadows of the use of telemedicine. However, most of the GPs surveyed agreed with the need for its further reimbursement.

Research has limitations, as does our study. First, data on rural/urban areas, gender and age of participants are missing. In addition to data protection considerations, the questionnaire was developed in the emergency state of the COVID-19 pandemic and focused on the GPs' perception of the use of telemedicine, considered at that time as a temporary alternative during the crisis. Second, the limit of having only a response rate of 51% is explained by the demanding period, in a country facing an acute shortage of health professionals and a lack of protective equipment, which has all distracted the doctors in our survey. Third, asking physicians to comment on patients' perceptions of the rapid transition from traditional to virtual visit is another limitation. As GPs are selected by people who enroll and want to remain on the list of practice for a long time, knowing their satisfaction with this new critical approach to healthcare is in the interest of both parties.

Future work should focus on creative and innovative solutions that integrate telemedicine as a complementary form of PHS delivery and streamline the management of general practice, not only as a temporary response to a crisis, but as a proactive method to increase access to quality care. Studies on the need for telemedicine-based training for family physicians can improve capacity building and research on patients' perceptions of virtual care can help to build trust and satisfaction.

Abbreviations

COVID,19, Coronavirus disease 2019; GPs, general practitioners; PHIH, Public Health Insurance House; PHA, public health authorities; PC, primary care; WHO, World Health Organization; ICT, information and communications technologies; AI, artificial intelligence.

Ethics Approval and Informed Consent

This study received the approval of the Ethics Committee of the College of Physicians from Cluj-Napoca, Romania, Nr. 984, April 7, 2020. The guidelines outlined in the Declaration of Helsinki were followed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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Abordarea paliativa a SIDA in era terapiei antiretrovirale si impactul in etica medicala

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Rezumat
Terapia antiretrovirala activa (AART) a revolutionat ingrijirea pacientilor infectati cu virusul imunodeficientei umane (HIV), a redus mortalitatea sindromului imunodeficientei dobandite (SIDA), conducand la cresterea prevalentei bolii. Aparitia SIDA ca noua boala amenintatoare de viata si conversia ei de la o evolutie rapid fatala la o boala cronica progresiva este o problema etica medicala provocatoare. Pentru multi bolnavi infectati HIV tratamentul antiretroviral a insemnat "conversia mortii la disabilitate", cu aparitia fazei de boala cronica. Nevoia integrarii ingrijirii paliative si curative este mai importanta in aceasta faza decit in era pre AART. Urmatoarea provocare in ingrijirea SIDA este abordarea multiplelor probleme psihosociale si etice. Contextul psihosocial al SIDA, izolarea, culpabilitatea, disperarea sunt provocari emotionale care adauga complexitate rolului ingrijirii paliative. Exista preocupari privind protectia societatii de pacientii SIDA si privind protectia pacientilor SIDA de societate. Asocierea SIDA cu saracia, cu unele minoritati etnice compun vulnerabilitatea acestor pacienti care necesita si interventii sociale. Chiar si in era terapiei antiretrovirale (AART) si in ciuda unor progrese in educatia publica, raman stigmatizarea si marginalizarea populatiei SIDA in societate. Este necesara centrarea ingrijirii pe pacient, spre deosebire de centrarea pe boala. Lectia invatata din ingrijirea bolnavilor oncologici trebuie aplicata la cea a tinerilor adulti suferinzi de afectiuni non-maligne fatale, cum este SIDA. Provocarile multiple ale SIDA au testat si rafinat etica medicala. Ea a fost orientata spre o recunoastere mai explicita a autonomiei personale, a respectului pentru confidentialitatea si consilierea pacientilor. Integrarea terapiei specifice HIV cu medicina paliativa in era AART trebuie abordata activ de catre personalul medical academic in instruirea studentilor si adresata atat profesionistilor medicali din ingrijiri paliative cat si a celor din ingrijirea specifica, antiretrovirala.
Cuvinte cheie: SIDA, terapie antiretrovirala, medicina paliativa, etica medicala.

In primii ani dupa 1980, SIDA a devenit cauza principala de deces a tinerilor adulti. Progresele in ingrijirea SIDA si in terapia specifica antiHIV, au condus la declinul mortalitatii in anii 1990, accelerat dupa introducerea inhibitorilor proteazei in 1996. Infectia HIV nu mai este o boala rapid fatala. Pacientii care pot tolera terapia antiretrovirala devin bolnavi cronici. Rezultatul este cresterea numarului pacientilor care traiesc cu SIDA, mai ales adulti tineri, prevalenta bolii fiind astfel in crestere. Acest pattern a fost mai marcant in tarile industrializate in care terapiile specifice HIV promise au fost realizate pentru multi bolnavi infectati HIV. Totusi, chiar si in era terapiei active anti-retrovirale (AART), SIDA ramine o importanta cauza de morbi-ditate si mortalitate in populatia adulta si atentia acordata problemelor de paleatie si de sfarsit al vietii este un aspect esential al ingrijirii.
Teme clinice majore care includ managementul durerii si a altor simp-tome, planificarea ingrijirii in faze avansate, problemele psihosociale sunt incluse in furnizarea ingrijirilor paliative pacientilor cu SIDA. Impactul tratamen-tului specific bolii asupra istoriei naturale a infectiei HIV a condus la o evolutie cu traiectorie variabila a bolii.
Pentru multi pacienti AART a insemnat "conversia mortii la disabili-tate", cu aparitia fazei cronice carac-terizate de exacerbari, remisiuni si eventual moarte, pentru ca timpul de supravietuire de la diagnostic la moarte s-a prelungit. Un aspect important in terapia pacientilor infectati HIV este in prezent mentinerea aderentei la tratament pentru prevenirea inductiei rezistentei virale. Intr-o perioada scurta de timp, infectia HIV a evoluat spre o traictorie tipica bolilor cronice, progresive, amenintatoare de viata.
Contextul psihosocial al bolnavilor SIDA adauga complexitate rolului ingrijirilor paliative. SIDA prezinta probleme psihosociale unice pentru pacienti, familie si furnizorii de ingrijiri paliative; este o boala amenintatoare de viata afectand adulti tineri, deseori cu multipli membrii ai

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familiei infectati, ridicand probleme dificile legate de moarte prematura, afaceri neincheiate, familie in dificultate, mosteniri nere-zolvate. Culpabilitatea, rusinea, furia si disperarea sunt provocari emotionale ale unei boli infectioase progresive, incura-bile. Unele comportamente legate de infectia HIV raman inacceptabile social in unele contexte, iar asocierea intre SIDA, saracie si unele minoritati etnice determina vulnerabilitatea acestor pacienti. In ciuda unor progrese in educatia publicului si a ingrijorarilor legate de SIDA, ramane un grad inalt de stigmatizare, frica, prejudiciu privind SIDA in cadrul societatii. In contextul modificarii filozofiei ingrijirii SIDA, medicina paliativa urmareste ameliorarea calitatii vietii in cadrul unui model in care obiectivele ingrijirii colaborative sunt dezvoltate de catre furnizorii de servicii paliative in acord cu pacientul si familia. Acest model accentueaza rolul comunicarii si al colaborarii si disponi-bilitatea de a accepta obiectivele pacientului ca si supreme (confortul, ameliorarea suferintei fizice si psihice, respectarea refuzului terapiei sau a intreruperii acesteia). Este de interes aceasta abordare colaborativa in care este impartasita incertitudinea evolutiei, cu multiple nuante si nici un raspuns clar si in care pacientii si terapeutii lor trec prin decizii dificile, incapabili de a controla rezultatul final. In acest mediu clinicienii au invatat sa munceasca impreuna cu pacientii si familiile lor pentru a clarifica obiectivele ingrijirii paliative: ameliora-rea calitatii vietii, oferirea suportului si confortului in a discuta complexitatea problemelor unei boli progresive, incura-bile. Obiectivele ingrijirii centrate pe nevoile pacientului si a familiei asigura decizii viitoare care nu vor neglija ingrijorarile importante ale acestora. Medicina paliativa este un domeniu cunoscut de peste 30 ani si recunoscut ca specialitate medicala de 20 ani. Este dezamagitor faptul ca ea este inca gresit inteleasa si insuficient reprezentata mai ales in tarile in curs de dezvoltare. Pionierii dezvoltarii medicinii paliative Cicely Saunders si Elizabeth Kubler-Ross au recunoscut importanta unei abordari mai umane a pacientilor incurabili si medicina paliativa ca un domeniu special al expertizei medicale. Desi marginalizata la inceput, medicina paliativa a devenit recunoscuta ca esentiala pentru calitatea ingrijirii furnizate pacientilor cu boli cronice, amenintatoare de viata. Declaratia de la Venetia privind Bolile Terminale, revizuita si extinsa in 2006, solicita medicii la implicare in reducerea suferintei si la actiune pentru protectia intereselor pacientilor lor cu bolile incurabile. Ea incurajeaza guvernele si institutiile de cercetare la a investi resurse in dezvoltarea tratamentelor de imbunatatire a ingrijirii la sfarsitul vietii, iar universitatile medicale sa includa predarea medicinii paliative in curricula lor.

Universitatea de Medicina si Farma-cie "Iuliu Hatieganu" Cluj-Napoca a avut initiativa si oportunitatea de a instrui in medicina paliativa 8 cadre didactice de la diferite catedre (medicina de familie, neurologie, psihiatrie, boli infectioase in Proiectul PHARE-Profesionisti in Ingri-jiri Paliative, Dundee, Marea Britanie, 1999-2000 si 2 cadre didactice au devenit formatori de formare in Medicina Paliativa dupa participarea la activitatile Proiectului European de Instruire Voca-tionala Leonardo da Vinci 2006, multi-centric in Londra, Liverpool si Lancaster. Instruirea a fost centrata pe managementul bolilor cronice non-maligne si pe abordarea multiprofesionala a ingrijirii paliative. Medicina paliativa a fost introdusa in curricula universitara si postuniversitara. Nevoile de ingrijire paliativa ale bolnavilor cronici non-oncologici au fost de mult timp recunoscute. Bolnavii cancerosi necesita ingrijiri paliative cu durata de saptamani sau luni, in timp ce suferinzii de SIDA si alte boli cronice non-maligne, evoluand cu insuficienta de organ necesita ingrijiri paliative de luni si ani. Bolnavii SIDA si cei care ii ingrijesc, membrii familiei, asistentii sociali, profesionistii medicali, sunt din ce in ce mai frustrati de obstacolele majore in furnizarea unei ingrijiri adecvate. Extensia ingrijirilor paliative la bolnavii non oncologici a fost de mult timp impiedicata de o combinatie de factori: prognostic incert al acestor afectiuni, dificultati financiare, lipsa specialistilor in medicina paliativa cu expertiza in bolile non-maligne si absenta evidentelor in relatie cu modelul adecvat de ingrijire. Profesionistii medicali, furnizori de servicii medicale specifice pentru bolnavii HIV au devenit inalt specializati si sunt mai putin atenti la problemele ingrijirilor paliative decit in prima faza a epidemiei. Nevoia ingrijirilor paliative pentru bolnavii SIDA continua paralel cu dezvoltarea noilor agenti terapeutici, iar disciplinele ingrijirilor paliative si managementul complex al SIDA au inca multe de invatat una de la cealalta. Aceste probleme trebuie sa fie abordate activ de catre ambele categorii de personal de ingrijire paliativa si specifica antiHIV. Calitatile clinice de compasi-une, empatie, de a inspira speranta fac o reala diferenta in viata celor suferinzi de boli cronice, amenintatoare de viata. Infectia HIV este

intens privata in transmisia ei, boala determinand izolare si devastarea vietii personale prin impac-tul ei. Ingrijirea paliativa a bolnavilor SIDA abordeaza teme clinice majore incluzand managementul durerii si al altor simpto-me, planul de ingrijire in faza avansata si problemele psihosociale. Provocarile viitoare in ingrijirea HIV/SIDA vor determina cresterea atentiei asupra multiplelor probleme psihosociale, orientata spre pacient, mai mult decat pe boala, inclusiv cele legate de sfarsitul vietii si perioada de doliu. Trebuie sa aplicam lectia invatata din ingrijirea bolnavilor cu cancer la numarul in crestere a tinerilor adulti suferinzi de boli non-maligne. Clinicienii isi vor modifica atitudinea de la un management de rutina al unei boli cronice la o abordare personalizata a ingrijirii paliative in paralel cu continuarea tratmentului, specific anti-retroviral. Vocatia medicala implica abilitati clinice esentiale - ascultare activa, respectarea autonomiei, o buna comunicare medic-pacient, continuitatea ingrijirii de durata care sunt importante si pot fi implementate oriunde in lume. Facilitarea unei morti "bune", demne, este la fel de importanta ca si diagnosticul si tratamentul.

Managementul durerii si a altor simptome ale bolnavilor HIV/SIDA. In faza avansata a bolii exista simptome considerabile ceeea ce sugereaza rolul important si permanent al interventiilor paliative. Ambele tipuri de interventii curative si paliative pot fi oferite nu atat pe baza unor algoritme diagnostice si ghiduri de tratament, cat mai ales in functie de prioritatile si valorile pacientului si ale familiei. Ingrijirile paliative ale bolnavilor SIDA constau in terapii directionate comorbiditatior infectioase si maligne legate de SIDA si tratamente centrate pe furnizarea confortului si controlul simptomelor. Ele implica servicii multidimensionale si multidisciplinare incluzand nursing, asistenta sociala, medicina complementara/alternativa si terapie fizicala. Medicina paliativa orienteaza ingriji-rea spre simptom si spre pacient si include urmatoarele: managementul simptomelor (fatigabilitatea, durerea), tratamentul efectelor adverse (greata, varsatura), suportul psihosocial (depresia, ingrijirea in faza avansata a bolii), ingrijirea la sfarsitul vietii. Durerea in SIDA a fost atribuita efectelor specifice infectiilor oportuniste (cefaleea din meningita criptococala, durerea abdominala viscerala din infectia diseminata cu complexul Mycobacterium avium-MAC), efectelor infectiei HIV insasi sau a raspunsului imun secundar (polineuropatia senzitiva distala, mio-patia din cadrul infectiei HIV), efectelor medicatiei specifice antiHIV (neuropatia periferica secundara terapiei dideoxinu-cleosidice, cefaleea secundara zidovudinei, tulburari gastrointestinale secundare inhibitorilor proteazei)sau efectelor nespecifice din cadrul bolilor cronice debilitante.

Din nefericire rezultatul declinului ratei mortalitatii SIDA si a supravietuirii prelungite este vulnerabili-tatea pacientilor cu aparitia unor noi complicatii, cum este neuropatia periferica. In plus, in timp ce incidenta durerii datorate infectiilor oportuniste a diminuat prin administrarea terapiei antiretrovirale active AART si a protocoalelor profilactice eficiente, unele medicamente utilizate in tratmentul HIV pot cauza durere si alte simptome compromitand eficienta tratamentului, daca aceste simptome nu sunt si ele tratate paliativ. Multe studii au demonstrat faptul ca durerea pacientilor SIDA este subdiag-nosticata si subtratata.

Ele reflecta recunoasterea insuficienta a durerii de catre multi medici si/sau rezistenta in a lua in considerare aprecierea durerii de catre pacienti cu istoric de abuz de substante. Indiferent de posibilele explicatii pentru subtratarea durerii rezultatul este ca pacientii SIDA sunt la risc de durere semnificativa si calitate a vietii diminuata, ceea ce poate fi prevenit printr-o evaluare si management adecvat al durerii. Asociat durerii, pacientii SIDA prezinta inalta prevalenta a altor simptome, mai ales, dar nu exclusiv in stadiile avansate ale bolii. Medicii frecvent identifica insuficient si deseori subtrateaza simptome comune ale pacientilor SIDA. Simptomele includ diverse simptome fizice si psihice: fatigabilitatea, anorexia, depresia, agitatia, anxietatea, greata, varsatura, diareea, tusea, dispneea, febra, transpiratii, prurit. Provocarile managementului simpto-melor au crescut odata cu prelungirea fazei cronice a bolii, recunoasterea toxicitatii cumulative a drogurilor la pacienti cu terapie anti-retrovirala de lunga durata.

Incertitudinea prognosticului si ingrijirile paliative in HIV/SIDA in era terapiei antiretrovirale (AART)

Prognosticul evolutiei bolii HIV/ SIDA este mult mai incert si mai putin predictibil decat era in perioada pre-antiretrovirala. In timp ce numarul limfo-citelor CD4+ si incarcarea virala sunt mijloace excelente pentru aprecierea raspunsului la terapie si a prognosticului general, accesul redus la terapia antiretrovirala eficienta, altereaza prog-nosticul bolnavilor SIDA

Ghidurile Organizatiei Hospice Nati-onale britanice din 1996 pentru aprecierea prognosticului in boli cronice non-maligne cert diagnosticate a incercat sa genereze criterii indicatoare pentru prognostic probabil de sub 6 luni in SIDA, subliniind necesitatea ingrijirii paliative.
Conditiile clinice sugestive pentru prognostic al bolii de sub sase luni sunt: limfomul SNC, criptosporidioza, slabirea severa, infectie diseminata MAC, sarcom Kaposi visceral, dementa SIDA avansata, toxoplasmoza, cardiomiopatia severa, diareea cronica severa. Markerii paraclinici sunt: numarul limfocitelor CD4 + <25 cells / mm, HIV ARN > 100000 copii / ml, albumina serica <2.5 gm / dl. O problema care apare frecvent in relatie cu complexitatea prognosticului si luarea deciziilor in SIDA in era AART este discontinuitatea terapiei anti-retrovirale la pacientii care fie nu raspund, fie mai probabil nu vor raspunde la tratament. Exista controverse privind decizia de a stopa terapia chiar si in fata aparentului esec al tratmentului pentru ca beneficiile supravietuirii trebuie evaluate in lumina impactului potential favorabil in prevenirea declinului viitor.
Recomandarile actuale si ghidurile de terapie anti-retrovirala in SIDA nu raspund la intrebarea privind renuntarea la terapie, ci includ doar initierea terapiei, reflectand centrarea pe tratament care defineste acum ingrijirea infectatilor HIV; exista totusi o nevoie importanta de a elabora ghiduri adecvate care sa includa si criteriile de intrerupere a terapiei antiretrovirale la bolnavii cu boala avansata si la muribunzi. In aceste situatii terapia antiretrovirala nu va avea mai probabil nici un beneficiu si va adauga confuzie si cost prin continuarea trata-mentului AART. Exista doua exceptii. Una este cea a pacientului in stare avansata de boala, dar cu incarcare virala inalta. Alta exceptie este situatia in care pacientul a investit mult emotional in continuarea terapiei antiretrovirale, incat este rezonabil sa fie continuata. Totusi este de subliniat ca aceasta este mai mult o decizie psiho-sociala decit medicala. Aceste exemple subliniaza inca o data importanta clarificarii obiectivelor tera-peutice, evaluarea potentialului impact si a posibilelor riscuri si beneficii. Munca in colaborare cu pacientii pentru determinarea prioritatilor si a planului terapeutic trebuie sa evite centrarea pe boala in locul orientarii spre pacient a interventiilor.
Inaintea introducerii terapiei anti-retrovirale, medicii au invatat cum sa-si insoteasca pacientii pe parcursul bolii, sa fie martori la suferinta si moarte. Noile posibilitati terapeutice trebuie sa nu determine omiterea ingrijirilor paliative din protocolul pacientilor pentru care terapia antiretrovirala nu mai este eficienta. Initial, in primii ani ai epidemiei SIDA in tarile dezvoltate, ingrijirea SIDA a fost paliativa, iar furnizorii de servicii medicale au fost prin definitie profesionisti in ingrijiri paliative.
Terapiile anti HIV/SIDA au evoluat rapid de la mijlocul anilor 1990 cand a crescut interesul privind terapia antiretrovirala si deciziile complexe legate de indicatiile ei. Cresterea "medicalizarii" ingrijirii SIDA se datoreaza partial progresului terapiilor eficiente care ofera posibilitatea controlului replicarii virale, dar si aparitiei acestei paradigme biomedicale ca rezultat al pierderii perspectivei asupra bolilor cronice progresive, incurabile. Provocarea actuala este evaluarea distincta a ambelor discipline, pentru a oferi pacientilor beneficiile celor doua tipuri expertize. Este important pentru profesionistii medicali implicati in ingrijirea bolnavilor HIV sa ramana sensibili la nevoile de ingrijire paliativa pe tot parcursul bolii.
Medicina paliativa are mult de oferit ingrijirii infectatilor HIV: cresterea aderentei la terapia antiretrovirala activa (AART) si la alte terapii, infruntarea complexelor probleme psihosociale ale pacientilor SIDA si a familiilor lor. Clinicienii pot beneficia de asemenea de interventii paliative bazate pe evidente care sunt eficiente ca adjuvante la terapia primara. Evaluarea clinica a prognos-ticului si rezultatelor este mai complexa acum decat era inainte si nevoia ingrijirilor paliative trebuie sa coexiste cu terapia specifica pe o perioada indelungata de timp.
In ciuda progreselor in terapia antiretrovirala este importanta recunoas-terea faptului ca dihotomia curativ vs. paliativ in ingrijirea SIDA este una falsa. SIDA este o boala cronica, progresiva care inca genereaza considerabila morbiditate si mortalitate, si nevoia integrarii abordarilor paliative si curative este chiar mai importanta decat in era dinaintea terapiei antiretrovirale. Exista de asemenea evidente ca ingrijirile la domiciliu si cele comunitare aduc beneficii in calitatea vietii pacientilor cu boli cronice avansate si conduc la o buna aderenta la regimurile de terapie antiretrovirala in timp. Era AART a evidentiat faptul ca fara sisteme de ingrijiri comunitare de lunga durata si fara dispensarizare corecta creste riscul rezistentei la drogurile antiretrovirale si pacientii devin "intratabili" prin multipla rezistenta

medicamentoasa.
Nevoia ingrijirii la sfarsitul vietii nu a disparut nici in era AART. HIV/SIDA raman in continuare cauze importante de deces si in viitor, astfel incat problemele legate de ingrijirea in faze avansate si terminale ale bolii nu vor putea fi evitate curand. In plus, tarile dezvoltate se confrunta in prezent cu decizii dificile legate de obiectivele ingrijirii, intreru-perea terapiei antiretrovirale, acceptarea esecului tratamentului si a mortii in era AART care sunt diferite de perioada dinaintea terapiei active antiretrovirale in care moartea era acceptata ca iminenta si universala. Aceste aspecte au devenit mai complexe si mai nuantate, implicand abordarea problemelor psihosociale si de ingrijire terminala care nu sunt familiare noii generatii de furnizori de ingrijire a bolnavilor HIV.
Impactul SIDA asupra eticii medicale in era terapiei antiretrovirale (AART)
Cresterea incidentei HIV/SIDA in anii 1980 a provocat multiple reflectii etice si a generat dezvoltarea politicilor de sanatate. Managementul bolnavilor SIDA a ridicat de asemenea probleme etice complexe.
Ingrijirea pacientilor SIDA este o provocare medicala dificila, dar si o provocare etica dificila. SIDA a stimulat mai multe dezbateri etice decit orice alta boala in istorie. Una dintre ingrijorari este cum sa protejam societatea de bolnavii SIDA (izolarea sau carantinarea pacientilor SIDA, discriminarea, scree-ning-ul populatiei tinta pentru anticorpi antiHIV, interventiile legale, inregistrarea victimelor si notificarea contactilor lor, protectia sangelui, proble-me care implica educatia si cercetarea.
O alta ingrijorare este cum sa protejam pacientii SIDA de societate, drepturile individului privind confidenti-alitatea, trimiterea si primirea informati-ilor si prescrierea terapiei. Consecinta interesului crescand legat de aceste aspecte este faptul ca populatia este mai bine informata si intelege mai bine complexitatea acestei boli.
Progresele terapiei antiHIV au ridicat probleme etice aditionale in special in relatie cu accesul la tratamentul activ antiretroviral. In ciuda costului ridicat al acestor tratamente, multe din tarile bine dezvoltate le-au putut face disponibile intregii lor populatii. Totusi marea majoritate a populatiei infectate HIV, adica 90%, traiesc in tari sarace, fara resurse si fara infrastructura pentru furnizarea acestei terapii. OMS si multe organizatii non guvernamentale au dezvoltat programe pentru cresterea accesibilitatii la tratament specific a bolnavilor din aceste tari, dar sunt necesare inca multe eforturi. Un obstacol major este protectia patent-ului oferit produselor farmaceutice, ceea ce impiedica producerea si distributia genericelor cu pret mult mai accesibil.
Alte probleme etice sunt ridicate de cercetarile privind un vaccin eficient anti HIV. Consideratiile etice ale prevenirii infectiei HIV si a cercetarii acestui vaccin sunt: design-ul trialurilor clinice, selectia populatiei participante, revizuirea etica a trialurilor propuse, protectia populatiei vulnerabile, utilizarea adecvata a placebo-ului, consimtamintul informat, supravegherea continua a participantilor la trial si includerea femeilor si a copiilor.
Problemele etice legate de sfarsitul vietii bolnavilor SIDA sunt de asemenea subiect de dezbatere. Managementul corect, adecvat al situatiilor dificile din stadiul terminal, integreaza expertiza tehnica cu orientarea umana si etica.
Sunt necesare cercetari privind identificarea, evaluarea si planificarea etapelor ingrijirii pacientilor suferinzi de boli cronice in evolutie spre deces si este nevoie de educatie care sa mentina treaza umanitatea si sensul vocatiei de medic. Aceasta este o provocare enorma a pietei de oferte de modele de ingrijiri de sanatate si care va conduce la selectia celui favorabil pacientilor cu boli cronice, amenintatoare de viata.

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1

Cross-Cultural Issues in Academic Palliative Medicine

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1. Introduction

1.1 The influence of cultural diversity in palliative medicine

The definition of culture, as an integrated pattern of learned beliefs and behaviors that include thoughts, styles of communicating, ways of interacting, values, practices, and customs has evolved, over time, but the underlying understanding is that culture is the lens through which people give the world meaning and which shapes their beliefs and behaviors. Culture is a system of shared ideas, concepts, rules and meanings that underlies the way we live – and approach death. Cultural diversity refers to more than ethnic diversity; age, gender, sexual preference, capabilities, education, place of residence, and occupation also contribute to diversity of culture. [Lickiss, 2003]. Cultures change or evolve over time and this affects many areas. In palliative medicine attitudes and practices regarding care of the incurable patient, of the dying (and dead) have changed, from unspeakable neglect common to the multiple contemporary patterns.[Kellehear , 2001]. The role of culture is significant in palliative care, and how it is conceptualized and applied has enormous consequences for patients, families and health care providers. It influences communication patterns, decision-making styles, responses to symptoms, treatment choices, and emotional expression at end of life [Valente, 2004; Werth et al, 2002]. Studies show that when cultural differences are inadequately addressed, inferior care occurs, affecting trust, and leading to patient dissatisfaction, nonadherence. [Betancourt & Green, 2010; Bruera et al., 2001; Ward et al., 2004]. The progress in palliative medicine requires balancing clinical art with science while paying due attention to cross-cultural differences that influence patients' and physicians' attitudes toward health care matters. The importance of cultural sensitivity for oncologists is now increasingly recognized and teaching and training in cultural competence are mandatory. [Betancourt & Green, 2010; Biasco & Surbone 2009].

1.2 Cross-cultural medical education and the need of cultural competence in the modern medical school

In the medical encounter of the multicultural universities, there is interaction between the culture of the medical students, the culture of the patients, and the medical culture that surrounds them. Physicians increasingly encounter patients of diverse racial, ethnic,

linguistic, and religious backgrounds, making effective cross-cultural communication skills essential. They should be sensitive to the diverse patients' health values that may be based on multiple cultures which they belong to (race, ethnicity. religion, gender, socioeconomic status, occupation, disability etc). The need for training in cultural competence is currently a requirement for medical schools. [Chun et al. 2010; Rodriguez et al. 2011]. Cultural competence refers to an ability to interact effectively with people of different cultures. It comprises four components: (a) awareness of one's own cultural worldview, (b) attitude towards cultural differences, (c) knowledge of different cultural practices and worldviews, and (d) cross-cultural skills.[Molinuevo & Torrubia, 2011]. Developing cultural competence results in an ability to understand, communicate with, and effectively interact with people across cultures.[Martin & Vaughn , 2007].

Cultural competency is something beyond the somewhat rigid categories of knowledge, skills, and attitudes: the continuous critical refinement and fostering of a type of thinking and knowing—a critical consciousness—of self, others, and the world. [Kumagai & Lypson, 2009]. As the european countries population and their universities become more diverse, racially and ethnically, demographic differences between physicians and patients increase, and the medical profession itself becomes more diverse, cross-cultural medical training takes on greater significance.[Rosen , 2004] .Cross-cultural education become important in preparing medical students in order to meet the health needs of the growing, diverse population. It has emerged because socio cultural factors are critical to the medical encounter.There are some medical universities which have been incorporated cross-cultural curricula into undergraduate medical education. [Betancourt, 2003; Betancourt, 2005; Davis & Smith, 2009].

The goal of these curricula is to prepare students to care for patients from diverse social and cultural backgrounds, and to recognize and appropriately address racial, cultural, and gender biases in health care delivery. Despite all changes, academic medical curriculums seldom prepare students for the realities of caring for patients with chronic progressive life threatening illnesses. An imbalance has been created in medical education which led to public concerns about poor communication and a perception that doctors lack care. [Taran, 2010]. The increasing attention to palliative medicine education has created major opportunities for improving education about care of the chronic progressive illnesses and for addressing multicultural issues in medical education. [Shanmugasundaram et al., 2009]. Medical schools offer some formal teaching about palliative and end-of-life care, but there is evidence that training is inadequate. [Lloyd-Williams & Macleod, 2004].

1.3 Motivating factors for cross-cultural medical education in palliative medicine

There are some motivating factors for cross-cultural medical education as folows:

- perception of chronic ,progressive illness, disease, causal factors, and treatment varies by culture
- diverse belief systems exist related to health, healing, and wellness
- culture influences attitudes toward health-care providers and motivations for seeking health care
- individual preferences and culture affect traditional and nontraditional approaches to health-care delivery and decision making

- communications between patient and health-care providers need to be clear and convey respect for individual beliefs and differences
- health-care providers in the delivery system are increasingly from culturally diverse and underrepresented minority groups
- patients have personal experiences of biases within health-care systems perceived as a reaction to their culture, ethnicity or religion

1.4 Spiritual dimensions of the health care in palliative medicine

Religious beliefs and practices are part of culture. Patients desire conversations with their health-care providers about spiritual and religious concerns. Physicians should ask about customs and practices, listen, explain and correct for their own cultural biases A good caring relationship is the greatest insurance against, and antidote for, the inevitable cultural mistakes.[Williams et al., 2011].

The advances of modern medicine increased life expectancy and this generated complex issues of the chronic progressive diseases' management. Increasing attention is being paid to the spiritual dimensions of the health care. The avoidance of the spiritual needs assessment in clinical practice and in the academic medical education may constitute a negligence and an important ethical issue. [Florea et al., 2008].

Palliative medicine and one of its core element, the spiritual care, provides a holistic patient-centered care applying a novel philosophy on living with incurable diseases and on death. Physicians, medical trainers mostly those using high medical technology and their students need special skills to communicate with patients and families. The compassionate care of the whole person-body, mind and spirit-has long been an ideal of medical education and practice. Many studies highlight the role that spirituality, culture, and end-of-life issues play in the future of medical education. [Azad, 2002; Betancourt, 2003; Betancourt 2006; Rosen et al. 2004].

Spirituality and religion, while often indistinguishable from culture, are beginning to be addressed in medical education, introducing palliative medicine module in medical schools curicula. A large segment of people claims belief in a higher being, and studies indicate that patients who have some religious commitment benefit in terms of stress reduction, recovery from illness, reduction of depression, and adjustment to disability. [Koenig et al., 2000 ; Lo et al., 2002; Williams et al., 2011 ; Wright, 2004] .

This evidence has provided the impetus among medical educators to include spirituality and health in undergraduate medical school curricula in order to increase sensitivity awareness about spiritual issues and to teach students communication techniques about different patients' spiritual beliefs, as they may affect their health and health care. Greater understanding of the diverse social, cultural, and spiritual contexts in which patients seek health care will facilitate more-favorable health outcomes and the cross-cultural medical education will have the potential to positively influence disparities in health. [Azad et al,.2002]. Some medical universities expand their students' and residents' education by integrating spirituality and medicine in the curriculum. Some of the europen and american medical schools, as our university, have been introduced courses in palliative medicine, including spiritual needs assessment and support, and many international hospitals have spiritual care initiatives.

Our university's undergraduate and postgraduate curriculum offer training in palliative care in a patient-centered model, including spiritual care and cultural diversity issues. Students are skilled in the understanding of human relationships, cultural sensitivity awareness in order to be able to integrate the personal meanings of values for both themselves and their patients, achieving a required cultural competence.

1.5 Obstacles to the inclusion of multicultural health content in the curricula of medical schools

To achieve the competence necessary to provide culturally appropriate education and culturally appropriate health care is a learning process that requires time, effort, practice, and introspection.

There are a number of obstacles to the inclusion of multicultural health content in the curricula of medical schools:

- difficulties in introducing new materials and experiences into an already overcrowded curriculum,
- lack of specialized teaching and learning resource materials,
- insufficient numbers of faculty prepared to teach the subject.

2. Methodology

The purposes of this study was to explore medical students' skills in cultural competence, their cultural sensitivity awareness, using 32 oncological outpatients with different cultural backgrounds, included in palliative care programs.

2.1 Recruitment process

2.1.1 Criteria for patients

Criteria for patients were a diagnosis of cancer and registration with a palliative care programme. The patient and family member had to be aged over 18 years, without obvious cognitive impairment as judged by referring health professionals. They had three different ethnicity (Romanian, Hungarian, German) and different religions (Orthodox, Catholic, Lutheran).

Patients designated the family member most involved in decision making regarding their illness (often but not necessarily the immediate carer) and from both of them formal consent was obtained.

2.1.2 Criteria for students

32 international students in the sixth year of their medical studies, from our university, were selected. They were from different cultural backgrounds: eight from United States, eight from Asia (two Chinese, four Indians, two Pakistani) eight from Africa (six Tunisian, two Moroccan) and eight from european countries (France, Germany, United Kingdom, Bosnia, Portugal).

Students attended the palliative medicine module as elective and all performed at least one summer practice in palliative care settings of their home countries.

The palliative medicine program included a number of six hours devoted to cultural sensitivity training. Methods that were used to integrate culturally sensitive topics into the curricula were: lectures, PBL (problem –based learning) cases with patients selected from three diferent romanian ethnic groups, creative teaching methods using simulated patients with diverse cultural backgrounds and small-group discussions.

All the students responded positively to our request to take part in an interview about palliative care, including spiritual care, even though most had before very limited knowledge of the subject.

2.2 Data collection and analysis

Students used a semistructured interview (one-to-one interview) (average one hour) with patients, focused on four basic dimensions in palliative medicine that vary culturally.

The four dimensions focused in the patients' interview were:

- communication of "bad news", eliciting detailed descriptions of patients' perceptions of their experiences of disclosure about the illness
- spiritual needs assessment: difficult subjects approach, recognizing symptoms and behaviors which may be related to spiritual pain and the relationship between pain and spiritual/psychological healing.
- locus of decision making
- attitudes toward advance directives and end-of-life care.

Semi structured interviews were selected because they are flexible, interactive, allow for deeper understanding of issues, and a greater exploration of cultural diversity issues. They are also dynamic and responsive to the language and concepts of individuals.

The students were divided into four focus groups. The focus groups were multi-cultural and included international medical students of different cultures to give a more diverse mix, palliative care professionals and medical teaching staff. Focus group discussions were effective in eliciting data on the cultural diversity of the patients and of the future physicians and in generating broad overviews of issues of concern to the cultural patient group.

A second interview was conducted with the same 32 international students in the sixth year of their medical studies, from our university, before and after they participated to palliative medicine module and group discussions.

All the students' interviews were personal meetings with teaching staff in palliative medicine that lasted about an hour and they took the form of a free and open discussion facilitated by a guiding questionnaire that had been drawn up in advance.

Some guidelines aimed at:

a. communication skills in different cultural environment :active listening,; common cultural variations regarding physician-patient communication; assess patients' knowledge of disease and prognosis; breaking bad news; strategies regarding ethnic, racial, and religious differences; common cultural variations regarding medical decision making; dealing with dificult questions ; eliciting and responding to patients' fears ; assessing spiritual needs as part of the initial assessment and ongoing care

b. student perception of palliative medicine module
c. student perception of cultural diversity, cultural sensitivity, cross-cultural issues integration in palliative medicine module

3. Results

3.1 Findings from patients' interviews

3.1.1 In the communication process with their patients, students appreciated:

- what are the patient's needs, with specific focus on information needs, views of patients in palliative care and family members regarding their experiences of disclosure and information sharing during the course of the illness
- how to identify common concerns or issues that might be used by students to shape and develop plans with respect to communication, with particular sensitivity to ethnic and cultural differences.

Patients and their relatives'need for sensitivity and respect for individual wishes in the communication process emerged as a central theme in the interviews. While this was especially important at the time of the initial disclosure, it recurred at all the different stages of information provision during the illness and affected the way in which content was perceived. The content needs most important to patients and families was related to prognosis and hope. Open communication regarding all aspects of the illness and its progress was reported as desirable by almost all participants, regardless of cultural backgrounds.

Almost all *patients,* 87% said they wanted to know the diagnosis of their illness. With four exceptions (in patients who shared information only in later stages) they thought it is important that information was fully shared with their families during all of the illness. A perception of insufficient information was reported to add stress, frustration, and uncertainty.

Of the respondents, 90% of the family members thought it was important for the patient to know the diagnosis. Three family members had requested that the patient must be not fully informed.

Students expressed different opinion: Bosnian, Indians, Pakistani and Chinese students expressed evasiveness regarding complete disclosure of the diagnosis to the cancer patients. They motivated their evasiveness with four reasons for nondisclosure:

- Bosnian culture believes that open discussion of serious illness may provoke unnecessary depression or anxiety in the patient
- Indians culture specifically views discussion of serious illness and death as disrespectful or impolite
- Chinese culture believes that direct disclosure may eliminate hope;
- Pakistani culture believes that speaking aloud about a condition, even in a hypothetic sense, makes death or terminal illness real because of the power of the spoken word.

In many Asian cultures, it is perceived as unnecessarily, cruel to directly inform a patient of a cancer diagnosis. Emotional reaction to news of serious illness is also considered directly

harmful to health. Indians, Pakistani, Chinese and Bosnian students preferred to act like "going around" the diagnosis and being indirect about serious illness in contrast to the emphasis on "truth telling" of the American students, whose directness they described as hurtful. Asian students' strategies commonly employed to minimize direct disclosure include using terminology that obscures the seriousness of a condition or communicating diagnostic and treatment information only to the patient's family members. Students agreed that, in certain cultures, while communication about serious illness and death may not be overt, information may be conveyed with subtlety. Facial expressions, voice tone, and other nonverbal cues may convey the seriousness of a patient's status without the necessity for explicit statements.

Most patients, 91%, wanted to know their prognosis, and family members respected their wish to know or not, although some would have wanted to protect the patient from details regarding prognosis.

All the students agreed to inform completely the patients and their relatives about prognosis in order to increase adherence to palliative care. They viewed information as a mechanism that enhanced decision making and keeping some control. Most patients wanted their family member present when they met health carers, although a small number expressed a desire to be the first to know or to control how much or when the family member should be told.

3.1.2 Spiritual needs assessment was a real challenge for the students

They used their spiritual-assessment skills (e.g., compassion, presence, and active listening) in understanding how spirituality affects health and appreciating the spiritual needs of patients from diverse cultural and spiritual backgrounds. Students identified as spiritual needs of their patients:

- to have the time to express true feelings without being judged,
- to speak of important relationships,
- to have hope,
- to deal with unresolved issues, to prepare for death.

They recognized spiritual pain as loss of meaning, loss of hope, loss of identity due to lost roles, lost activity, lost independence. Its characteristics identified by the medical students were: constant and chronic pain, insomnia, withdrawal or isolation, conflict with family members, friends or medical staff, anxiety, fear, mistrust of family, friends, physicians, hospice staff, depression, hopelessness, feeling of failure with life.

Despite most of the students considered themselves to be not religious or slightly religious and the heterogeneity in self-reported faith traditions: Christian (n = 7), Hindu (n = 4), atheist (n = 5), Catholic

(n = 6), Jewish (n = 2), Muslim (n = 8) they recognized the appropriate conditions which recommend clergy involvement. The specific situations identified to make referrals to chaplains as part of the interdisciplinary team were:

- when spiritual issues seem particularly significant in the patient's suffering,
- when spiritual/religious beliefs seem of particular help and support for the patient,

- when addressing the spiritual needs of a patient exceeds the physician's comfort level,
- when specific community spiritual resources are needed,
- when physician or nurse suspect spiritual issues which the patient denies,
- when the patient's family seems to be experiencing spiritual pain,
- when the medical staff (doctors, nurses, students) seems to be experiencing spiritual pain or is in need of support – multiple deaths, issues of injustice, particular attachment to a dying patient.

In the feedback gathered from patients, the majority of the participants (95%) felt their symptoms management needs and spiritual needs had been addressed and viewed their interaction with the students involved in palliative care positively. According to patients' responses, the majority wanted their doctor to be interested in their spiritual care.

3.1.3 Locus of decision making

With regard to decision making, american students emphasised on patient autonomy which contrasted with preferences for more family-based, physician-based, or shared physician- and family-based decision making among Indians and Tunisian students'opinion. Pakistani students shared that in their culture, physicians may be adopted into the family unit and addressed as parent, aunt, uncle, or sibling.

European students emphasised that in their culture patients prefer that physicians, because of their expert knowledge, make independent decisions to reduce the burden on patients and their families.

In group discussions, the students discussed choices regarding strategies for managing disease, approaches to symptom relief, or partnership in facing profound existential issues and facilitating personal growth. Decision making involved ethical principles (understood in the light of cultural sensitivity), with considerations of autonomy, justice, beneficence, and maleficence.

3.1.4 Attitudes toward advance directives and end-of-life care

Concerning the advance directive completion, this had lower rates among romanian patients of specific ethnic backgrounds, which may reflect distrust of the health care system, current health care disparities, cultural perspectives on death and suffering.

Chinese students emphasised that in their culture, people are less likely to sign their own do-not-resuscitate (DNR) orders because of its negative emotional impact on health.

By paying attention to the patient's values, spirituality, and relationship dynamics, students elicited cultural preferences. They actively developped rapport with ethnically diverse patients simply by demonstrating an interest in their cultural heritage.

3.2 Findings from students' interviews

3.2.1 Initial students' feedback, before palliative medicine module attendance

They discussed their self-perceived learning needs in dealing with patients with advanced diseases and different cultural backgrounds. Of the respondents 81 % students considered

that they were not prepared for all the skills/competencies needed to approach cultural diversity issues in palliative care. We identified many common themes and concerns emerged from students' interviews, including:

- lack of knowledge about palliative care and lack of understanding about spiritual care,
- confusion as to the difference between spiritual and religious needs,
- concern about how healthcare and social services would relate to spiritual care, finding a way to develop spiritual care and successfully integrate it into the general health and social services systems.

3.2.2 Interviews after students completed this module

They shared their educational and training experiences and made suggestions about cultural diversity issues in palliative care management and its influence in learning environment. Most students respondents (96%) thought that general communication skills, e.g. communicating with patients and patients' relatives, counselling skills such as dealing with difficult questions, eliciting and responding to patients' and relatives' fears, breaking bad news, crosscultural issues were well covered in the paliative medicine module and group discussion.

Focused was on:

- communication issues, including disclosure and consent;
- modes of decision making: how or when is the patient or family involved
- concepts of disease, meaning of pain and other symptoms;
- agree priorities with patients with different cultural backgrounds
- fulfil patients' needs for information about treatment
- attitudes to medication (especially opioid drugs and sedatives) and to nutrition
- ways of conceptualising death and dying in relation to the rest of life
- understand issues which surround euthanasia
- spiritual matters, as well as religious issues, including rituals.
- customs surrounding death, burial or cremation, and bereavement
- supporting a bereaved person, preparing family for bereavement.

According to students' responses after palliative medicine training the approach of spiritual care has had a positive and meaningful impact. Students identified two important facilitators of spiritual care: having time, unencumbered by competing clinical demands and effective communication with the patients and their family members. There were also identified the implications for medical care of the spiritual and religious issues:

- if the patient religion forbid any specific parts of medical care (transfusion, surgical therapies),
- barriers to patient-physician communication posed by religion/spirituality complex issues,
- the patient refuse to discuss spiritual or religious implications of his health care.

Students'evaluation before and after this module demonstrated improvement in students' abilities to assess patients' palliative care needs and spiritual needs and negotiate issues regarding complex treatments. They appreciated the interactive nature of palliative

medicine program and described it as relevant, balanced, and practical. Students were interested in finding out about new ways to enhance the lives quality of the patients and families in distress and they wanted better understand the challenges facing the development of palliative care. More attention may need to be directed towards the learning environment. The majority of respondents medical students showed that the patient's culture is an important issue when providing care (with 95 % of indicating "moderately important" or "very important"). In the interviews the students also explored educational issues in palliative medicine. They considered the attendance to palliative medicine module as an improved clinical experience and an opportunity for cultural sensitivity and cultural competence achievements. Medical students achieved interviewing skills, abilities to work in a multidisciplinary team, to pay attention to complementary treatments and ethical aspects of cross-cultural issues. Some critical attributes of good communication they identified as important: playing it straight, staying the course, giving time, showing you care, making it clear, and pacing information. They affect the quality of the relationship between health professionals and patients and their families and should be emphasised in the teaching of communication skills. Communication of prognosis to patients with cancer is a sensitive issue and therefore patients' needs for information should be individually assessed. Most students, 91% considered that poorly handled cross-cultural issues may have negative clinical consequences, including longer office visits, patient noncompliance, delays obtaining informed consent, ordering of unnecessary tests, and lower quality of care. A significant proportion of the respondents, 82% thought that they had developed some attributes fully through their work experience in palliative medicine module and group discussions and these were opportunities to consolidate what they had learned in the previous years. The teaching staff involved in this activities appreciated the open-mindedness attitudes, which made students especially receptive to our educational programme.

4. Discussions

The diversity of the cultural and racial orientations of the people means that those who provide health and social services increasingly interact with others of diverse cultural, social, racial, linguistic, and religious backgrounds.[*Green et al,* 2008]. The public is better informed and it has a better understanding of the complexity management of the chronic, life-threatening diseases. [Florea et al, 2008]. Given rapidly changing global demographic dynamics and the evidence regarding health outcomes attributable to cultural competence education, it is time to consider the approach to preparing medical students to reduce health disparities and care for ethnoculturally and socially diverse patients.

In an effort to provide health care professionals with the knowledge and skills to effectively care for diverse populations, an educational movement in "cross-cultural care" has emerged. This field has received a new emphasis during the past 10 years as a result of statements made by the American Medical Association (AMA) and the Accreditation Council for Graduate Medical Education, among others, that crosscultural training is necessary for the effective practice of medicine in this globalizing world.[Weissman, 2005]

The issue of cultural competence training is an evolving element of medical education curricula which must answer to the following questions:

- How can medical curricula be developed so that content is relevant and applicable to the workplace and graduates acquire the personal characteristics and skills required for medical practice?
- What are the obstacles to providing undergraduates with well-managed work experience, adequate exposure to the real world of medical practice and the necessary opportunities to apply knowledge and acquire essential skills, attitudes and personal attributes?

Tomorrow's physicians must be adequately trained to provide optimal care to patients from ethnic, social, spiritual and religious backgrounds different from their own. [Nelda &Valmi, 2011].

Cultural competence translate into improved health outcomes and reduction of disparities in health or health care. [Betancourt , 2006]. Improving student–patient communication is an important component of improving the quality of care generally, and addressing differences in quality of care that are associated with patients' race, ethnicity, or culture more specifically. Many students are unfamiliar with common cultural variations regarding physician-patient communication, medical decision making, and attitudes about formal documents such as code status guidelines and advance directives. End-of-life discussions are particularly challenging because of their emotional and interpersonal intensity. [Far, 2002; Kuin et al 2006; Mueller et al, 2001].

Introducing palliative medicine modules in undergraduate medical education is an important opportunity to enhance students with cultural sensitivity awareness and cultural competence. Despite recent progress and educational efforts, there are attitudinal barriers still thwart the successful integration of palliative care into general medical education. Medical students and residents are uncomfortable facing death and dying. The prevailing medical culture continues to view death as a medical failure. Palliative care, despite its growing scientific base, is often perceived as low-tech or ''soft.'' Many trainees do not view palliative care skills as core clinical competencies. They learn to prescribe antihypertensive and hypolipemiants drugs but they fail to master the use of opioids. These attitudes may contribute to practice patterns that tend to devalue the provision of palliative care even though the public increasingly asserts the importance of humane medical care at the end of life.

Previous efforts in cultural competence have aimed to teach about the attitudes, values, beliefs, and behavior of certain groups. There is no "manual" of how to care for patients from different racial, ethnic, or cultural groups; instead, a more effective approach is to learn about how social, cultural, or economic factors influence patients' health values, beliefs, and behaviors. [Gundersen, 2000; Hibnall & Brooks 2001; Hudson, 2006; Koenig, 2000].

In our study, group discussions were focused on the issues that arise most commonly due to cultural differences, cultural sensitivity. International students' curiosity, empathy, and respect, as well as an understanding of the romanian multiethnic patient's social context, motivated their interest in achieving cultural competence. We approached the concepts of cultural competence and"transnational competence" in medical education, which are not new concepts and have been argued previously, resulting in greater adoption of these principles among medical educators.[Gregg & Saha, 2006].

These principles have now become the blueprint for teaching medical students throughout the country, although adoption of this approach is slow but steady. [Koehn & Swick , 2006]. Training under this approach may be especially helpful in the care of patients who come from cultures different from the culture of the clinician. [Betancourt & Green, 2010]. Cultural competence aims to bridge the "cultural distance" that exists between medical providers and their patients.

Medical students and tomorrow's physicians need a practical set of tools and skills that will enable them to provide quality care to patients everywhere, from anywhere, with whatever differences in background that may exist.

The field of cultural competence aims to assure that health care providers are prepared to provide quality care to diverse populations. There are evidence highlighting the fact that the failure of health care providers to acknowledge, understand, and manage sociocultural variations in the health beliefs and behaviors of their patients may impede effective communication and better patient care. [Betancourt & Green, 2010]. The diversity of the cultural and racial orientations of the people means that those who provide health and social services increasingly interact with others of diverse cultural, social, racial, linguistic, and religious backgrounds. Transnational competence in medical education offers a comprehensive set of core skills derived from international relations, cross-cultural psychology, and intercultural communication that are also applicable for medical education. [Koehn & Swick, 2006].

There is an effort to change the medical education systems. Moderate gains in cultural sensitivity training, such as inclusion of the topic in curricular objectives and content were made. These changes are part of an increased institutional commitment in some medical schools to improve students' abilities to provide culturally sensitive clinical care when they become practicing physicians. Gaps continue to exist in teaching this important skill. To achieve cultural competence, an organized and systematic approach of the objective development, curriculum planning, learning methods, and program evaluation is needed. [Betancourt & Green, 2010; Lie et al., 2006].

In some medical schools informal teaching of culturally sensitive topics have occurred. It is possible that medical students and faculties from different cultural backgrounds learn from each other using students' mobilities and teaching staff's professional mobilities and share their beliefs and attitudes with respect to health practices on an informal basis. Exposure to patients from other cultural backgrounds in practice, as our international students did, might bring culturally sensitive issues to the individual learner. Cultural competency involves an understanding and acceptance of cultural practices and is more than simply being able to speak the same language. Communicating effectively across cultures is a critical factor in providing quality health care to diverse populations. Becoming culturally competent is an ongoing process and a lifelong commitment.

Neglecting cultural issues in palliative medicine should be a possible source of tension in family and of confusion to health professionals. Sensitivity to the cultural nuances of communication (the breaking of bad news), family dynamics, decision making, interpersonal tensions and suffering may add value to attempts to care. Cultural gaps between health professionals and patients are expressed in many ways (from treatment preferences to concepts of spirituality). Bridging the gaps may require long time to be accomplished. This must begin in medical students' training.

As an effort to provide physicians training with the knowledge and skills to address cross-cultural challenges in the clinical encounter, curricula in "cultural competence" have emerged and been integrated into medical education. Cultural competence is a developmental process at both the student and university levels. With appropriate support, students can enhance their cultural awareness, knowledge and skills over time. Cultural strengths exist within our university and they will be better tapped in the training process of our 2800 international medical students, from 50 countries. A process of cultural competence assessment will be developped and students will benefit by heightening awareness, influencing attitudes toward practice, and motivating the development of knowledge and skills. This process also benefits the university by informing planning, policy-making, resource allocation and training/professional development activities. A growing literature delineates the impact of sociocultural factors, race, ethnicity and ethical issues on palliative care. [Florea et al., 2008; Shanmugasundaram et al., 2009; Williams et al., 2011].

Sociocultural differences between patient and physician influence communications and clinical decision making. Medical students and physicians aren't shielded from diversity, as patients present varied perspectives, values, beliefs, and behaviors regarding health and well-being. These include variations in patient recognition of symptoms, thresholds for seeking care, ability to communicate symptoms to a provider who understands their meaning, ability to understand the prescribed management strategy, expectations of care (including preferences for or against diagnostic and therapeutic procedures), and adherence to medical interventions and medications. Evidence suggests that provider-patient communication is directly linked to patient satisfaction and adherence and subsequently to health outcomes. [Betancourt, 2003]. Thus, when sociocultural differences between patient and provider aren't appreciated, explored, understood, or communicated in the medical encounter, patient dissatisfaction, poor adherence, and poorer health outcomes result.

The cultural competence, transnational competence approach will promote advances in preparing medical students to reduce health disparities among patients with multiple and diverse backgrounds, health conditions, and health care beliefs and practices. In palliative care this consistently directs attention to the policy and social factors, as well as the individual considerations, that can alleviate suffering and enhance health in a globalizing world.

Palliative and end-of-life care for a patient born and living in an Anglo-Saxon country may be different from that of a patient in a Latin or Islamic country, as patients' relationships with individual physicians and with institutions, preferences and practices of truth telling, attitudes toward screening, prevention and clinical trials, decision-making styles, and end-of-life choices are all subject to cultural variability. Additional research on how cultural diversity influences patients' and families' preferences in regard to palliative care is needed to meet the needs of different communities and individual patients.[Biasco & Surbone 2009].

Our study, like others, [Chun etal.,2010; Thompson et al, 2010] suggests that specific education, rather than individual experience of crosscultural interactions, which may not always be positive, is needed to improve the cultural competence of tomorrow's physicians and future palliative care professionals. The introduction of humanism, medical ethics and multiculturalism into medical education involves linking the professional training of students with human values, an orientation of education and practice towards addressing human needs and interests. [Kumagai & Lypson, 2009]. We need research to identify, assess,

and plan the care of all patients who are sick enough to die, and we need education that keeps alive our humanity and sense of vocation. This is an enormous challenge on the market of healthcare models, but one that will be useful to the chronic, life-threatening ill patients. [Florea et al, 2008].

5. Conclusions

The chapter describes the experiences of international medical students involved in palliative care programme, addressing cross-cultural issues, cultural sensitivity awareness. It draws attention to the complex relationships between different patients' and students' cultural background and palliative care issues and to the need of cultural competence in medical education.

Six-year international students at our medical school appreciated the level to which cultural competence instruction in palliative medicine occurred.

Our sudy also revealed that it is not only the patient's culture that matters; the students' and tomorrow's physicians' culture is equally important. Teaching about palliative care from a crosscultural perspective was favorably received by students and positively influenced students' attitudes.

Palliative medicine training is a complex opportunity of cross-cultural medical education which must be approached and this will increase the cultural competence and standards of the academic medical education. Our findings indicate that multicultural medical education in palliative medicine is an important area for future research and curricular reform.

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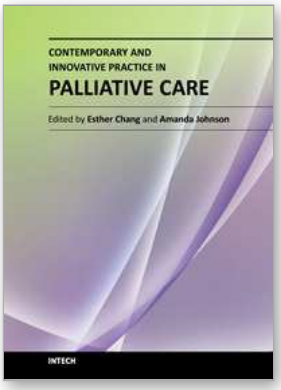

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This book is designed to provide a comprehensive insight unto the key and most prevalent contemporary issues associated with palliation. The reader will find viewpoints that are challenging and sometimes discerning, but at the same time motivating and thought-provoking in the care of persons requiring palliation. This book is divided into three sections. Section 1 examines contemporary practice; Section 2 looks at the challenges in practice; Section 3 discusses models of care. This book is an excellent resource for students, practising clinicians and academics. By reading the book, reflecting on the issues, challenges and opportunities ahead, we hope it will create within the reader a passion to take on, explore and further develop their palliative care practice.

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