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Construction and validation of a Bundle for evaluation of thyroid function in patients with cirrhosis

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HIGLIGHTS

- Thyroid dysfunction has been reported in association with several chronic diseases, including advanced liver disease.
- The bundle discussed here is aimed at proposing systematic assistance according to the best evidence-based practices available.
- The process of constructing and validating the bundle was carried out in the following stages: a) bibliographic survey; b) bundle elaboration; and c) content validation.
- The bundle was considered valid to facilitate medical decision making, aiding physicians to manage, in a practical and effective manner, the thyroid function of patients with liver cirrhosis.

ABSTRACT – Background – Thyroid dysfunction has been reported in association with several chronic diseases, including advanced liver disease. This disease and its management are often neglected in clinical practice. The bundle discussed here is aimed at proposing systematic assistance according to the best evidence-based practices available. **Objective –** To construct and validate a bundle to evaluate thyroid function in patients with liver cirrhosis. **Methods –** The process of constructing and validating the bundle was carried out in the following stages: a) bibliographic survey; b) bundle elaboration; and c) content validation. The bibliographic survey was carried out in an integrative review about evidence related with the thyroid function of patients with liver cirrhosis. The findings from the integrative review were considered as supporting evidence for the elaboration of the bundle. The tool then created used accessible language and was evidence-based, ensuring that information was based on current literature. **Results –** The bundle was restructured to provide guidance on the management of patients with liver dysfunctions, including: cirrhosis due to general causes, cirrhosis due to hepatitis C, non-alcoholic fatty liver disease, primary biliary cholangitis, and hepatocellular carcinoma. The orientations in the bundle included: exams to be requested to screen for thyroid disorders, and guidance about the treatment of these dysfunctions and their associated complications. We analyzed specialist evaluation of the bundle using the Content Validity Index (CVI). We carried out a binomial test to evaluate consistency and specialist agreement regarding the items in the bundle, considering values >0.61 as a good level. The items in the bundle were considered to be valid (CVI >0.80). The general CVI of the instrument was 0.95 (CI95%: 0.91–0.98). **Conclusion –** The bundle was considered valid to facilitate medical decision making, aiding physicians to manage, in a practical and effective approach, the thyroid function of patients with liver cirrhosis. This tool should not be used as a replacement for individual, evaluation of the physician providing assistance. We recommend the structured bundle to be added to medical practice, considering its simple application, low cost, and potential to contribute for the management of these patients.

Keywords – Liver cirrhosis; thyroid disease; clinical protocols; validation study.

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INTRODUCTION

Liver cirrhosis has become one of the main health issues around the globe. According to the Global Burden of Disease, from 2017, it has caused 1.32 million deaths and represented 2.4% of deaths in the world[1]. According with the World Health Organization (WHO), liver cirrhosis is the 11th cause of death worlouild[2].

Its main complications include: hemorrhage from varicose veins, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular carcinoma, hepatorenal syndrome, hepatopulmonary syndrome, and thyroid dysfunction[3].

There is a strong mutual influence associating the liver and the thyroid. The dysfunction of thyroid hormones (TH) can compromise liver processes, such as cholesterol metabolism. On the other hand, the liver is one of the main organs responsible for the peripheral TH metabolism. In general, most patients with liver disease are clinically affected by euthyroid sick syndrome. Advanced liver disease can manifest in changes in the laboratory profile of TH through the Euthyroid Sick Syndrome (ESS), which, in some cases, is indistinguishable from primary thyroid diseases[4]. The most consistent profile of the TH dysfunction in cirrhosis patients is low total and free T3 (TT3 and FT3, respectively), and elevated reverse T3 (rT3) levels. These alterations are similar to those from ESS, probably reflecting a low deiodinase type 1 (D1) activity, leading to a reduced conversion of T4 into T3. In more serious cases, when liver failure is imminent, the data is variable and low total T4 (TT4) levels can reflect the reduced synthesis of thyroxine-binding globulin (TBG) in the liver. In patients with chronic hepatitis associated with Primary Biliary Cholangitis (PBC), autoimmune thyroid disease is more prevalent[5].

Still, there are gaps in the knowledge about the role of liver dysfunction in the thyroid hormones, and how this can have a negative impact on the clinical progression of patients with liver disease.

The thyroid function has been a prognostic marker of liver disease, and hormone changes found in the thyroid usually revert when liver function improves[6].

By the term bundle we understand a "package" of care, aimed at systematically proposing assistance according to the best evidence-based practices available[7,8]. This research aims to construct and validate a bundle to evaluate thyroid function of patients with liver cirrhosis.

METHODS

Participants

This is a methodological search aimed at constructing and validating a bundle to evaluate thyroid function in patients with liver cirrhosis. The construction and validation period of the bundle was from June to July 2021. The validation stage of the bundle included 11 health workers with the following specialties: physicians specialized in gastroenterology and endocrinology with expertise in liver transplantation; and physicians from other specialties who attend patients with thyroid disease or liver cirrhosis. The research project was approved by the Research Ethics Committee of a high-complexity hospital center in the Brazilian Northeast on June 08, 2021, protocol approval 4.760.576.

Stages of the research

The process of constructing and validating the bundle was carried out in the following stages: a) bibliographic survey; b) bundle elaboration; and c) content validation[9].

Integrative review

The bibliographic survey was carried out through an integrative revision of the evidence related with thyroid function in liver cirrhosis patients. It was conducted in the databases Medline/Pubmed, Lilacs, Scopus, and Cochrane Library. The research question was determined according to the PICO strategy (P=Problem, I=Phenomenon of Interest, C=Comparison, O=Outcome)[10]. In this research, the "P" represented chronic lesions in the liver; the "I", the thyroid function; the "C" did not apply in the context; and the "O" referred to the impact of hepatic lesion on thyroid function.

Construction and validation of the bundle

The findings from the integrative review were seen as data to support the construction of the first

version of the bundle, whose main target audience are liver transplant surgeons and physicians who specialized in endocrinology and gastroenterology. The idea is to develop more effective strategies to screen for thyroid dysfunction in patients.

The bundle was structured according to the following needs: providing guidance about the management of these patients and potential complications; transmitting information about the exams to be requested in the screening for thyroid dysfunction; providing guidance on the treatment recommended for thyroid dysfunction (medication or conservative management); instructing about how to conduct patient follow up; and describing guidance to be provided by the physicians.

The scientific evidence that supported the construction of the banner was classified according to the hierarchy proposed by Melnyk and Fineout-Overholt[11]: I. for systematic reviews and meta-analyses of randomized clinical trials; II. for randomized controlled trials; III. for non-randomized controlled trials; IV. for case-control or cohort studies; V. for systematic reviews of qualitative or descriptive studies; VI. for qualitative or descriptive studies; and VII. for the opinion of authorities and/or reports from expert committees.

Specialists were classified using Guimarães et al.[12] criteria, whose goal is to select experts for validation studies, valuing their clinical and academic experience. Scores considered: experience in direct assistance and as a professor; published articles; participation in research groups; and residency, MS, and PhD in the fields of interest. Scores are summed up and categorized in an ascending order, where: junior expert = 5 points or more; master expert = from 6 to 20 points; senior expert = more than 20 points. All categories are eligible to participate in the study, but senior experts are preferred, followed by master experts.

Professionals were found through the Currículo Lattes, a platform that gathers curricula from Brazilian researchers. We also contacted the *Associação Brasileira de Transplante de* Órgãos (ABTO - the Brazilian Association of Organ Transplant) through email. This is a civil, non-profit medical association that aims to encourage all activities related with organ transplant and donation in Brazil. These strategies were used to find professionals who worked in large liver transplant services in the different Brazilian regions.

These professionals were invited through e-mail. Those who accepted were sent the first version of the bundle and the evaluation instrument[13], which was divided in three blocks: a) Block 1: objective; b) Block 2: structure and presentation; c) Block 3: relevance. The instrument must be answered through a Likert-type scale with the following options: 1-Inadequate; 2-Partially Adequate; 3-Adequate; 4-Completely Adequate. At the end of the instrument, there was a field for the evaluator to write any suggestions, corrections, and recommendations they saw fit.

Statistical analysis

The quantitative analysis of the validation of the bundle was carried out using the Content Validity Index (CVI), which measures the proportion or percentage in which specialists agree about the items and general aspects evaluated, making it possible to analyze items individually or collectively[14].

The CVI is calculated by adding up the answers of participants to questions in blocks 3 and 4. Then, this result is divided by the total number of responses. A cutoff point of 0.80 is recommended[15]. In this research, the CVI of each item of the bundle evaluation instrument was calculated, as well as that of the blocks and the total CVI[15].

To analyze the items in the bundle in depth, binomial distribution was calculated using the exact test, which is recommended for small samples. The level of statistical significance considered was $P>0.05$, and the proportion of 0.80 was the parameter to evaluate the CVI statistical reliability[16].

RESULTS

Integrative review

The 20 selected studies were published from 1983 to 2021. Most were published in the years 2012 (n=3), 2015 (n=2), and 2016 (n=3). Regarding their country of origin, most studies came from Turkey (n=3); the United States (n=2); Brazil (n=2); India (n=2); China (n=2); and Egypt (n=2). Regarding the type of study, most were prospective (n=8) (level of evidence IV), followed by cross-sectional ones (n=4) (level of evidence VI) (TABLE 1).

TABLE 1. Characterization of integrative review studies.

Variables	N	%
Country of origin		
Turkey	3	15.0
United States	2	10.0
Brazil	2	10.0
India	2	10.0
China	2	10.0
Egypt	2	10.0
Iran	1	5.0
Italy	1	5.0
Pakistan	1	5.0
Germany	1	5.0
Japan	1	5.0
Netherlands	1	5.0
Taiwan	1	5.0
Year of publication		
1983	1	5.0
2001	1	5.0
2003	1	5.0
2011	1	5.0
2012	3	15.0
2015	2	10.0
2016	3	15.0
2017	2	10.0
2018	2	10.0
2019	2	10.0
2020	1	5.0
2021	1	5.0
Type of study		
Cross-sectional	4	20.0
Prospective	8	40.0
Retrospective	2	10.0
Case-control	5	25.0
Clinical trial	1	5.0
Subject		
Cirrhosis from general causes	5	25.0
Cirrhosis from HCV	5	25.0
Non-alcoholic fatty liver disease	6	20.0
Primary biliary cholangitis	2	10.0
Hepatocellular carcinoma	2	10.0

Specialist characterization

Thirty-six specialists were invited through the Currículo Lattes platform. Furthermore, the ABTO e-mail contacted 1,857 specialists, 425 of them opened the e-mail and 12 accessed the form's content. There was a total of 12 respondents. One respondent was excluded, as she was not in accordance with our inclusion criteria (she was not a physician). The final sample, thus, was formed by 11 specialists (CHART 1). TABLE 2 shows the classification of specialists in accordance with Guimarães et al.[11]. Most were classified as master experts (n=7).

Validation of the bundle's content and appearance

An analysis of the CVI of the items used to evaluate the bundle found that all items were validated (CVI >0.80). In the individual CVI analysis, the items "The information is well structured regarding orthography and concord" and "The size of the font of the title and the topics is adequate" showed the lowest value (CVI =0.82). Still, the value was within the cutoff point considered for these items to be validated (CVI >0.80). The general CVI of the instrument was 0.95 (CI95%: 0.91–0.98) (TABLE 3). CHART 2 shows the final (post-validation) version of the bundle.

DISCUSSION

The prevalence of TH anomalies in cirrhosis patients varies from 13 to 61%[17]. The most commonly observed laboratory manifestations in these cases include low FT3, normal TSH, and high rT3, which are common in ESS[18,19]. As the severity and length of the disease increase, TT4 serum levels become subnormal[18].

Selected studies show an inverse relation between the FT3 level and the severity of liver dysfunction as evaluated using Child-Pugh and MELD[20-23]. Regarding the signs of severe liver cirrhosis, low FT3 levels are related with a greater incidence of complications such

CHART 1. Specialist classification.

Specialists	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11
Score	14	7	16	12	20	17	8	40	21	21	11
Classification	Master	Master	Master	Master	Master	Master	Master	Senior	Senior	Senior	Master

TABLE 2. Specialist characterization.

Variables	N	%	Mean (SD*)
Age (years)			39.3±7.8
Gender			
Female	7	63.6	
Male	4	36.4	
Time since graduation (years)			15.3±7.6
>10	7	63.6	
Titles			
Residency or specialization	6	54.5	
MS	2	18.2	
PhD	3	27.3	
Current occupation			
Direct care	2	18.2	
Teaching and direct care	3	27.3	
Teaching and research	1	9.1	
Direct care, teaching and research	5	45.4	
Works with thyroid dysfunction patients			
Yes	9	81.8	
No	2	18.2	
Experience (years)			9.3±8.6
Works with cirrhosis patients			
Yes	11	100	
No	0	0	
Experience (years)			10±7.8
Works with care for patients prior to liver transplant			
Yes	9	81.8	
No	2	18.2	
Experience (years)			7.2±5.3
Participates in research groups about thyroid dysfunction, cirrhosis, and/or liver transplant			
Yes	6	54.5	
No	5	45.5	
Experience (years)			5.4±9.0
Has publications in the field of thyroid dysfunction, cirrhosis, and/or liver transplantation			
Yes	8	72.7	
No	3	27.3	
Type of publication			
Abstract in annals, book/book chapter	1	11.1	
Scientific article, abstract in annals, presentation of work/lecture, book/book chapter.	4	44.4	
Scientific article, presentation of work/lecture, book/book chapter	1	11.1	
Abstract in annals	1	11.1	
Work presentation/lecture	1	11.1	

*SD: standard deviation.

TABLE 3. Validation of the content of the bundle.

Instrument items	*CVI	**CI95%		*P*-value
		Lower limit	Upper limit	
Block: Goals	1.00	0.72	1.00	0.09
1. The information/content is pertinent to the needs of the target audience in regard to this issue.	1.00	0.72	1.00	0.09
2. Information/content can help specialized physicians to carry out evaluations of thyroid function in patients with liver cirrhosis.	1.00	0.72	1.00	0.09
3. Promotes and/or encourages the use of new practices, including behavior and attitude changes in physicians in the assistance of liver cirrhosis patients.	1.00	0.72	1.00	0.09
4. Can be shared within its scientific field.	1.00	0.72	1.00	0.09
5. Attends to the goals of institutions that attend/work with the target audience.	1.00	0.72	1.00	0.09
Block: Structure and presentation	0.97	0.91	0.99	<0.001
1. The bundle is appropriate for its target audience.	1.00	0.72	1.00	0.09
2. The messages are presented clearly and objectively.	1.00	0.72	1.00	0.09
3. Information presented is scientifically correct.	0.91	0.59	1.00	0.32
4. The material is appropriate for the scientific level of the target audience.	1.00	0.72	1.00	0.09
5. The content is provided in a logical sequence.	1.00	0.72	1.00	0.09
6. Information is well structured in regard to orthography and concord.	1.00	0.72	1.00	0.09
7. The writing style is in accordance with the scientific level of the target-audience.	1.00	0.72	1.00	0.09
8. The size of the font of the title and the topics is adequate.	0.82	0.48	0.98	0.62
9. The number of pages is adequate.	1.00	0.72	1.00	0.09
Block: relevance	0.89	0.78	0.96	0.65
1. The topics portrait key aspects that should be reiterated.	0.82	0.48	0.98	0.62
2. The bundle allows generalization and the transference of knowledge in many contexts.	0.91	0.59	1.00	0.32
3. The bundle proposes the construction of knowledge.	0.91	0.59	1.00	0.32
4. The bundle addresses the topics essential to increase the level of knowledge of the target audience.	0.91	0.59	1.00	0.32
5. The bundle is adequate to be used by any physician specialized in the care for patients with liver cirrhosis.	0.91	0.59	1.00	0.32
General bundle CVI	0.96	0.92	0.98	–

*CVI: Content Validity Index; **confidence interval of 95%.

CHART 2. Final version of the bundle to evaluate the thyroid function of patients with liver cirrhosis.

Bundle to evaluate the thyroid function of patients with liver cirrhosis				
Clinical conditions	**Exams**	**Thyroid dysfunction impact on cirrhosis**	**Conduct**	**Levels of evidence/ Referrals**
General cause severe cirrhosis cases (Child-Pugh B/C and/or MELD >20).	Request TSH, FT4, and FT3 exams. In case of suspected Euthyroid Sick Syndrome (ESS): consider reverse T3. Most common laboratory standard of main thyroid dysfunctions: 1.ESS: -Low total and/or free T3; -Normal or low FT4; -Normal or high TSH; -High reverse T3.	Low FT3 as a possible factor for worse prognosis in liver disease. More severe cases, considering the Child-Pugh scale, especially B, C, and MELD, especially above 20 years old, in addition to risk for complications such as ascites, encephalopathy, and hemorrhagic varicose veins, in addition to laboratory markers of INR, albumin, PGT, bilirubins, and platelets in patients with low FT3 level.	Correlate low FT3 levels with the severity and prognosis of liver cirrhosis. Do not treat FT3 in isolation. In case of Euthyroid Sick Syndrome, evaluate thyroid hormones after liver transplant or cirrhosis stabilization to check whether normality was achieved. When suspecting primary thyroid disease, check observations at the end of the bundle*.	IV Novis, Vaisman e Coelho (2001) Penteado et al. (2015) Mansour-Ghanaei et al. (2012) Verma et al. (2017) Kayacetin, Kisakol e Kaya (2003) Shakoor, Kaneez e Iftikhar (2012) Taş et al. (2012) Punekar, Sharma e Jain (2018) Manka et al. (2019) Piantanida et al. (2020)

CHART 2. Continuation.

Clinical conditions	Exams	Thyroid dysfunction impact on cirrhosis	Conduct	Levels of evidence/ Referrals
Cirrhosis from Hepatitis C (CHC)	Request TSH, FT4, and FT3 exams. If the TSH is high, consider asking for anti-thyroperoxidase (anti-TPO) and anti-thyroglobulin (anti-TG) tests; In case of suspected Euthyroid Sick Syndrome (ESS): consider reverse T3. Most common laboratory standard of main thyroid dysfunctions: 1.ESS: -Low FT3; -Normal or low FT4; -Normal or high TSH; -High reverse T3. 2. Associated with the C virus: -Higher prevalence of thyroid autoantibodies.	Patients with cirrhosis due to HCC seem more likely to have positive results for anti-TPO and anti-TG antibodies, and hypothyroidism. Cases are more severe according with Child-Pugh and MELD scales in patients with low total and free T3.	Carefully monitor thyroid function during the follow up of patients with HCC infection. Evaluate thyroid hormones after liver transplant or cirrhosis stabilization to check whether normality was returned. Correlate low FT3 levels with the severity and prognosis of the liver cirrhosis. Do not treat FT3 in isolation. When suspecting primary thyroid disease, check observations at the end of the bundle*.	VI Antonelli et al. (2006) Piantanida et al. (2020) Yang et al. (2011) Novis, Vaisman e Coelho (2001) Mansour-Ghanaei et al., (2012) Verma et al. (2017)
Non-alcoholic fatty liver disease (NAFLD)	Request TSH, FT4, and FT3 exams. In case of suspected Euthyroid Sick Syndrome (ESS): consider reverse T3. Most common laboratory standard of main thyroid dysfunctions: 1.Associated with NAFLD -High or borderline-high TSH; -Normal or low FT3; -Normal or low FT4; 2.ESS: -Low FT3; -Normal or low FT4; -Normal or high TSH; -High reverse T3.	NAFLD patients have higher TSH levels. Hypothyroidism may be associated with higher risks for NAFLD and for non-alcoholic steatohepatitis (NASH) or fibrosis. Levothyroxine supplementation may have a positive effect over NAFLD in patients with clinical or mild subclinical hypothyroidism and dyslipidemia.	Correlate low FT3 levels with the severity and prognosis of liver cirrhosis. Correlate low FT3 levels with fibrosis and advanced non-alcoholic steatohepatitis (NASH). Supplement levothyroxine in patients with severe subclinical hypothyroidism** (TSH>10 mUI/L) to improve clinical characteristics of the metabolic syndrome and potential impact in NAFLD control. Consider supplementing levothyroxine in patients with mild subclinical hypothyroidism (TSH between the upper limit and 10 mUI/L) with NAFLD and dyslipidemia, with a potential beneficial effect over the prevalence of NAFLD. Check general observations for the treatment of subclinical hypothyroidism** When suspecting primary thyroid disease, check observations at the end of the bundle*.	VI Tahara et al. (2019) Kim et al. (2018) Liu et al. (2017) Bano et al. (2016)
Primary biliary cholangitis (PBC)	Request TSH, FT4, FT3, and anti-TPO exams. In case of suspected Euthyroid Sick Syndrome (ESS): consider reverse T3. Most common laboratory standard of main thyroid dysfunctions: 1. Associated with primary biliary cholangitis: -Higher prevalence of thyroid autoantibodies (anti-TPO) 2.ESS: -Low FT3; -Normal or low FT4; -Normal or high TSH; -High reverse T3.	Hypothyroidism is commonly found in PBC. The presence of thyroid dysfunction does not seem to influence on the rate of hepatic complications or PBC natural history.	Suspect PBC in patients with cholestatic liver disease and autoimmune thyroiditis. Regularly check thyroid function of patients with euthyroid sick syndrome with positive thyroid autoantibodies. In case of Euthyroid Sick Syndrome, evaluate thyroid hormones after liver transplant or cirrhosis stabilization to check whether normality was achieved. When suspecting primary thyroid disease, check observations at the end of the bundle*.	VI Elta et al. (1983) Floreani et al. (2016)

CHART 2. Continuation

Clinical conditions	Exams	Thyroid dysfunction impact on cirrhosis	Conduct	Levels of evidence/ Referrals
Hepatocellular carcinoma (HCC)	Request TSH, FT4, and FT3 exams. In case of suspected Euthyroid Sick Syndrome (ESS): consider reverse T3. Most common laboratory standard of main thyroid dysfunctions: 1.Associated with HCC: -Higher prevalence of clinical*** and subclinical** hypothyroidism; -Normal or high FT3. 2.ESS: -Low FT3; -Normal or low FT4; -Normal or high TSH; -High reverse T3.	Correlation between clinical*** or subclinical** hypothyroidism with worse advanced HCC prognosis. High prevalence of hypothyroidism in advanced HCC patients.	Correlate the presence of hypothyroidism with worse HCC prognosis Treat clinical hypothyroidism before specific HCC medication is started. Evaluate the need for subclinical hypothyroidism treatment**. When suspecting primary thyroid disease, check observations at the end of the bundle*.	IV Sahin et al. (2020) Shao, Cheng e Hsu (2021)

General observations	Evidence level/ references
There is a biological variation in TSH levels. Levels can increase as a result of stress, transitory diseases, and with age. This biological variation in TSH levels means that the finding of abnormal TSH levels should be followed by another blood test to confirm diagnosis. Patients with TSH > 10 mUI/L may have underlying thyroid disease. *In case of suspected primary thyroid disease, evaluate the need for anti-TPO test and thyroid ultrasound. Positive results for thyroid autoantibodies (anti-TPO is the most sensitive) and, in some cases, hypoechoic, non-homogeneous patterns found in the ultrasound can provide evidence for autoimmune thyroiditis. Consider the institution or adjust levothyroxine replacement in patients with already established clinical and subclinical hypothyroidism. Some medication can interfere on the interpretation of thyroid hormones, such as diuretics, glucocorticoids, beta blockers, amiodarone, interleukin-2, interferon alpha, among others. Consider thyroid ultrasound and antibodies dosage in case of doubt in the diagnosis.	VII Jonklaas et al. (2014) Bekkering et al. (2019) Pearce et al. (2013) Garber et al. (2012) Nice et al. (2019) Burch (2019) Vilar (2020) Piantanida et al. (2020)
**Subclinical hypothyroidism - serum TSH above normal range, combined with normal FT4 levels. Applicable when the thyroid function has been stable for weeks or longer, the hypothalamus-pituitary-thyroid is normal, and there is no current or recent severe illness. In this case, consider the following clinical management: TSH > =10 mUI/L: - Age <70 years: treat. - Age > =70 years: consider treatment in case of hypothyroidism symptoms or high cardiovascular risk. TSH <10 mUI/L: consider treatment in case of hypothyroidism symptoms, positive anti-TPO, or evidence of atherosclerotic cardiovascular disease, cardiac failure, or risk factors for these diseases. Observation: in patients aged >70 years with TSH <7 mUI/L, keep patient under observation.	
***Clinical hypothyroidism - TSH above normal range and FT4 below normal range. Consider adding or adjusting levothyroxine replacement in clinical hypothyroidism patients. Dosage adjustments are carried out according with serum TSH determinations 4–8 weeks after the beginning of the therapy or dosage adjustments.	

Captions: anti-TG: anti-thyroglobulin; anti-TPO: anti-thyroperoxidase, PBC: Primary Biliary Cirrhosis; HCC: hepatocellular carcinoma; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; HCV: Hepatitis C Virus; TH: Thyroid Hormones; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease; ESS > Euthyroid Sick Syndrome; FT3: Free Triiodothyronine; TT3: Total T3; FT4: Free Thyroxine; OGT: Oxaloacetic Glutamic Transaminase; PGT: Pyruvic Glutamic Transaminase; TSH: Thyroid-Stimulating Hormone.

as ascites, hepatic encephalopathy, and hemorrhagic varicose veins[19]. Verma et al.[24] found a significant correlation between low FT3 levels and hyponatremia in patients with liver cirrhosis. Manka et al.[25] discovered FT3 values significantly correlated with hepatic disease indices, including INR, PGT, billirubins, and platelets. There were no significant differences in TT4, TSH, and FT4 serum levels, when compared between Child-Pugh A, Child B, and Child C groups[6,24,26].

A common cause of chronic liver disease and cirrhosis is non-alcoholic fatty liver disease (NAFLD), whose global prevalence is 24%, with 31% in South America and 24% in the United States[27]. The NAFLD is a wide spectrum histologic disease that can be categorized as simple steatohepatitis, nonalcoholic steatohepatitis (NASH), portal fibrosis, cirrhosis, and can even progress into hepatocellular carcinoma (HCC) in later stages. TSH level can be an important risk fac-

tor for the development and progression of NAFLD, regardless of thyroid hormones[28]. Patients with NAFLD have significantly higher TSH levels, regardless of thyroid hormones, showing that hypothyroidism was associated with high risks for NAFLD[29] and progression into fibrosis, even with normal FT4 levels[30].

A study from Manka et al.[25] confirms there is a strong correlation between FT3 levels and substitute markers of hepatic fibrosis in patients with NASH. Specifically, the lower the FT3, the higher the probability that the individual will develop fibrosis, as indicated by a higher fibrosis score (NAFLD fibrosis score, NFS[1]) and increased hepatic rigidity. FT3 levels can also be in conformity with the normal rate (that is, low normal FT3 levels).

Reduced thyroid function was associated with a higher risk for advanced fibrosis. An explanation for this association is that higher TSH levels are associated with metabolic abnormalities, such as dyslipidemia and obesity. In this study, the association of subclinical NASH hypothyroidism and advanced NASH-related fibrosis continued to be significant after adjusting for obesity, metabolic risk factors, and insulin resistance, suggesting that subclinical hypothyroidism is an independent predictor of NASH and advanced fibrosis related with NASH.

Implementing levothyroxine replacement therapy in patients with subclinical hypothyroidism and dyslipidemia can reduce NAFLD prevalence. Results that support this outcome were more emphatic in severe subclinical hypothyroidism (TSH > =10 mUI/L) when compared to its milder form[29]. Benefits from levothyroxine replacement therapy in fatty liver disease have also been found in patients with subclinical hypothyroidism[31].

Cirrhosis patients are under risk for progression into HCC. Shao, Cheng e Hsu[32] evaluated the thyroid function of patients with HCC. Before any systemic therapy observed that 20% of them were found to have clinical or subclinical hypothyroidism. Hypothyroidism patients had a significantly worse global survival (GS) rate than patients with no hypothyroidism (median, 5.5 vs 11.6 months P=0.043). Hypothyroidism, be it clinical or subclinical, was associated with bad prognosis, even after other potential prognostic factors were adjusted for.

Regarding the correlation between autoimmune thyroid dysfunction and cirrhosis, evidence suggest autoantibody presence as a marker of thyroid disease, especially in the case of biliary cholangitis. Nonetheless, the presence of thyroid dysfunction does not have any impact on the rate of hepatic complications or the natural history of primary biliary cholangitis[33].

A limitation of this study was the fact that no validation was conducted with the target audience. We suggest further research to validate this bundle, and to evaluate the impact of its use in clinical practice.

CONCLUSION

We developed a bundle with information to facilitate managing thyroid dysfunction in patients with liver cirrhosis. This tool used accessible language and was based on scientific evidence to ensure that information was in accordance with up-to-date literature.

The bundle was considered to be valid regarding its appearance and content, with a general CVI of 0.95. It can be used in health services to aid in the physicians decision making, so they can provide diagnoses and efficiently evaluate the thyroid function of liver cirrhosis patients.

This tool should not be used as a replacement for the individual, autonomous evaluation of the physician providing assistance. We recommend incorporating the structured form into gastroenterology outpatient service care and in pre-liver transplant care, due to its ease of application, low cost, and potential to contribute with the management of these patients.

Authors' contribution

Montenegro AXCB and Dallago CM contributed to the conception or design of the study/research. Montenegro AXCB, Martins-Costa MC, Brasil IRC and Dallago CM contributed to the analysis and/or interpretation of data. Montenegro AXCB, Martins-Costa MC, Brasil IRC and Dallago CM contributed to the final revision wit critical and intellectual participation in the manuscript.

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Montenegro AXCB, Martins-Costa MC, Brasil IRC, Dallago CM. Construção e validação de um *Bundle* para avaliação da função tireoidiana em pacientes com cirrose hepática. Arq Gastroenterol. 2023;60(2):230-40.

RESUMO – Contexto – A disfunção tireoidiana tem sido relatada em associação com várias doenças crônicas, incluindo a doença hepática avançada. O seu reconhecimento e manejo são, muitas vezes, negligenciados na prática clínica. O bundle consiste em um pacote de cuidados, com a finalidade de promover a assistência de forma sistematizada, a partir da melhor prática baseada em evidências. **Objetivo –** Construir e validar um bundle para avaliação da função tireoidiana em pacientes com cirrose hepática. **Métodos –** O processo de construção e validação do bundle foi realizado a partir das seguintes etapas: a) levantamento bibliográfico; b) elaboração do bundle; e c) validação do conteúdo. O levantamento bibliográfico foi realizado a partir de revisão integrativa sobre as evidências relacionadas à função tireoidiana em pacientes com cirrose hepática. Os achados encontrados na revisão integrativa foram considerados como subsídios para construção do bundle. A ferramenta construída se baseou em evidências científicas, de forma a garantir informação pautada em literatura atual e com linguagem acessível. **Resultados –** O bundle foi estruturado com base nas seguintes finalidades: fornecer orientações sobre o manejo de pacientes com disfunção hepática, categorizado por: cirrose por causas gerais, cirrose por vírus da hepatite C, doença hepática gordurosa não alcoólica, colangite biliar primária e carcinoma hepatocelular. As orientações do bundle incluíram: exames a serem solicitados no rastreio dos distúrbios tireoidianos; orientações sobre indicação de tratamento destas disfunções e possíveis complicações associadas. A análise da avaliação do bundle pelos especialistas foi realizada a partir do cálculo do Índice de Validade do Conteúdo (IVC). Foi feito o cálculo do teste binomial para avaliar a concordância e consistência dos especialistas em relação aos itens do bundle, aceitando-se como bom nível o valor >0,61. Os itens do bundle foram considerados validados (IVC >0,80). O instrumento apresentou IVC geral de 0,95 (IC95%: 0,91–0,98). **Conclusão –** O bundle foi considerado válido para facilitar a tomada de decisão para o médico conduzir, de maneira prática e efetiva, o manejo da função tireoidiana em pacientes com cirrose hepática. Defende-se que a ferramenta não deve ser utilizada em substituição à avaliação individualizada e autonomia do médico assistente. Recomenda-se que a forma estruturada seja incorporada ao atendimento médico tendo em vista a fácil aplicabilidade, o baixo custo e o potencial para contribuir com o manejo desses pacientes.

Palavras-chave – Cirrose hepática; doença da tireoide; protocolos clínicos; estudo de validação.

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