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ORIGINAL ARTICLE

The effect of different definitions of hepatic injury on incidence and mortality rates in the ICU patient population with secondary hepatic injury☆☆

Gül Gürsel[a], Ayshan Mammadova[b,*], Eda Macit Aydın[a], Zeynep Çınar[a], Nurgül Navruzvai[b], Sümeyye Kodalak[b]

[a] *Gazi University School of Medicine, Critical Care fellowship program, Ankara, Turkey*
[b] *Department of Pulmonary Critical Care Medicine, Gazi University School of Medicine, Ankara, Turkey*

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KEYWORDS
Hepatic injury;
ICU;
Incidence;
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Definition;
SOFA;
Cholestasis

Abstract
Objective: The aim was to investigate how different hepatic injury (HI) definitions used in the same study population change incidence and mortality rates and which would best diagnose secondary HI.
Design: Single-centre retrospective observational cohort study.
Setting: Tertiary hospital ICU, ANKARA, Turkey.
Patients: Four hundred seventy-eight adult patients were included in the study.
Interventions: None.
Main variables of interest: Three definitions of HI were compared. Taking the SOFA hepatic criteria (SOFA: Total bilirubin (TBL) > 1.2 mg/dl) as the gold standard, sensitivity, specificity, positive and negative predictive values, and accuracy of the modified 2017 definition by the American College of Gastroenterology (ACG) and the 2019 European Association for the Study of the Liver (EASL) were calculated.
Results: Incidence rates ranged from 10% to 45% according to the definition ($p < 0.005$), while mortality rates ranged from 38% to 57%. When the SOFA1.2 (TBL > 1.2 definition was taken as the gold standard, the diagnostic value of the ACG definition was high, and HI was found to be an independent risk factor that increased mortality four times.

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* Corresponding author.
E-mail address: aysenmammadova665@gmail.com (A. Mammadova).

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Conclusions: According to this study's results, the incidence and mortality rates of secondary HI vary greatly depending on the definition used. A definition that includes minimal increases in ALT, AST, and TBL predicts mortality with reasonable incidence rates.
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PALABRAS CLAVE
Lesión hepática;
UCI;
Incidencia;
Mortalidad;
Definición;
Colestasis

El efecto de diferentes definiciones de lesión hepática sobre las tasas de incidencia y mortalidad en la población de pacientes de la UCI con lesión hepática secundaria

Resumen
Objetivo: El objetivo fue investigar cómo las diferentes definiciones de lesión hepática (HI) utilizadas en la misma población de estudio cambian las tasas de incidencia y mortalidad y cuál diagnosticaría mejor la HI secundaria.
Diseño: Estudio de cohorte observacional retrospectivo de un solo centro.
Ámbito: UCI del hospital terciario, ANKARA, Turquía
Pacientes o participantes: Se incluyeron en el estudio 478 pacientes adultos.
Intervenciones: Ninguna.
Variables de interés principals: Se compararon tres definiciones de HI. Tomando los criterios hepáticos SOFA (SOFA: Bilirrubina total (TBL)>1,2 mg/dl) como estándar de oro, sensibilidad, especificidad, valores predictivos positivos y negativos y precisión de la definición modificada de 2017 por el Colegio Americano de Gastroenterología (ACG) y se calcularon los de la Asociación Europea para el Estudio del Hígado (EASL) de 2019.
Resultados: Las tasas de incidencia oscilaron entre el 10% y el 45% según la definición (p < 0,005), mientras que las tasas de mortalidad oscilaron entre el 38% y el 57%. Cuando se tomó la definición SOFA1.2 (TBL > 1.2) como estándar de oro, el valor diagnóstico de la definición ACG fue alto y se encontró que HI era un factor de riesgo independiente que aumentaba la mortalidad cuatro veces.
Conclusiones: Según los resultados de este estudio, las tasas de incidencia y mortalidad de la HI secundaria varían mucho según la definición utilizada. Una definición que incluya aumentos mínimos de ALT, AST y TBL predice la mortalidad con tasas de incidencia razonables.
Publicado por Elsevier España, S.L.U.

Introduction

Secondary hepatic injury (HI) without underlying liver disease is the most common form of hepatic dysfunction in intensive care unit patients and increases morbidity and mortality.[1–4] Hypoxic liver injury, cholestasis, and drug-induced liver injury (DILI) are the most frequent forms of secondary HI in critically ill patients.[5–7]

While the definition of HI influences the incidence and mortality rates, there is no standard definition for critically ill patients. Many studies use the definition of bilirubin >2 mg/dl in the SOFA score.[8] On the other hand, previous studies have shown that elevated alanine aminotransferase (ALT) or aspartate transaminase (AST) above the upper limit of normal (ULN) is associated with increased mortality.[9] For this reason, other studies use 2 to 3-fold elevation of AST, ALT, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) to define it.[10]

Earlier studies used the definition of cholestasis instead of the definition of hepatic injury, and this definition is quite variable in the literature. While some studies have used total bilirubin levels greater than 2 mg/dL as a cutoff, others prefer a 2 to 3-fold elevation of ALP and/or GGT to define cholestasis.[11]

The importance of this problem is evident from the heterogeneity of definitions used in studies conducted during the COVID-19 pandemic and the difficulty in interpreting and generalising their results. The reported prevalence of liver injury in COVID-19 patients varied widely across studies, ranging from 5% to 78%. For this reason, it has generally been concluded that the results of these studies cannot be adapted to clinical practice.[12–14]

On the other hand, while having a standardised definition of HI is essential, no study compares HI definitions and investigates the ideal description in the ICU patient population. This study compares HI definitions and their relationship with incidence and mortality rates in the same ICU patient population with secondary HI and investigates the most reasonable definition.

Methods

This single-centre retrospective observational cohort study was performed in a University Hospital Medical ICU between 2015 and 2019. The research protocol was accepted by the Gazi University ethics committee (number 869/2020), and informed consent was waived due to its retrospec-

tive design. Adult (>18 years old) patients were included in the study. For patients with multiple admissions, only the first one was considered. Exclusion criteria: Patients with acute liver failure, chronic liver disease, and preexisting liver failure. Patients with bone metastases or using drugs such as filgrastim that increase leukocyte alkaline phosphatase. Demographics, admission diagnosis, usage of vasopressors, renal replacement therapy, mechanical ventilation during ICU stay, ICU infections, cardiac arrest history, medications, main laboratory results on ICU admission and during the stay, and hospital survival rates of the patients were recorded. The presence of any shock (septic shock, cardiogenic, obstructive, hypovolemic), acute respiratory failure, acute kidney injury, neutropenia, or cardiac arrest was also recorded.

Secondary HI was defined based on three different definitions: occurrence during ICU admission and ICU stay. ALT, AST, ALP, GGT, and total bilirubin (TBL) levels were recorded during hospital admission.[8,15,16]

Definitions

In this study, we compared three definitions of HI: SOFA hepatic criteria (SOFA-1.2: TBL > 1.2 mg/dl), the 2017 definition by the American College of Gastroenterology (ACG), and the 2019 European Association for the Study of the Liver: DILI definition (EASL). We also calculated the severity of HI in all patients according to these definitions.[8,15,16] In this study, we took the SOFA-1.2 score as the gold standard.

To define if HI is cholestatic, hepatocellular, or mixed, we used the Roussel Uclaf Causality Assessment Method (RUCAM) classification and calculated the R ratio. The R ratio is calculated by the formula R = (ALT/ALT ULN)/(ALP/ALP (ULN) with an R ratio of >5 defined as hepatocellular injury,<2 cholestatic injury, and 2–5 mixed pattern.[17]

RUCAM is widely used in assessing the causality of drug-induced liver injury. The RUCAM system assigns points for clinical, biochemical, serologic, and radiologic features of liver injury, giving an overall assessment score that reflects the likelihood that the hepatic injury is due to a specific medication. We used this definition only to calculate and determine the biochemical pattern of liver injury, such as hepatocellular, cholestatic, and mixed, not to do causality assessment and DILI diagnosis.

Although it is recommended that the TBL criterion be used to diagnose HI, no threshold value was given in the ACG definition. We modified the ACG definition into four subgroups to find the definition with the best incidence and mortality rates and an independent risk factor for mortality. ACG definition was evaluated in four ways: ACG1, ACG2, ACG3 and ACG4 according to the inclusion of borderline (AST and ALT, elevation as <2xULN) criteria and two different TBL levels (1.2 and 2 mg/dL).

Original ACG definition

Borderline: AST and ALT, elevation as <2xULN, **Mild:** AST and ALT, elevations as 2–5xULN, **Moderate:** AST and ALT, elevations as 5–15xULN, **Severe:** AST and ALT elevations as >15xULN, and **Massive:** AST and ALT elevations as >10,000 IU/l.[15]

Modified ACG definition according to the inclusion of borderline criteria and two different TBL levels:

ACG1: AST and ALT, elevation as <2xULN and TBL > 1.2 mg/dL

ACG2: AST and ALT, elevation as <2xULN and TBL > 2 mg/dL

ACG3: AST and ALT, elevations as 2–5xULN and TBL > 1.2 mg/dL

ACG4: AST and ALT, elevations as 2–5xULN and TBL > 2

The third definition we used was the EASL 2019 DILI definition. The severity of HI classified according to EASL Clinical Practice Guidelines: Drug-induced liver injury.[16] Patients who met at least mild HI criteria were considered as having HI. Our aim in using the EASL definition was not to identify patients with DILI but to use a standard definition to compare different definitions. For this reason, causality assessment was not performed on the patients, and we cannot claim that patients with HI, according to this definition, have DILI.

We calculated and compared the incidence and mortality rates of each definition.

Drug Induce Liver Injury Severity Classification (reference 16).

Category International DILI	Severity Expert working group	Description
1	Mild	ALT ≥ 5 or ALP ≥ 2 and TBL < 2xULN
2	Moderate	ALT ≥ 5 or ALP ≥ 2 and TBL ≥ 2xULN, or symptomatic hepatitis
3	Severe	ALT ≥ 5 or ALP ≥ 2 and TBL ≥ 2xULN or symptomatic hepatitis and 1 one of the following criteria - INR ≥ 1.5 - Ascites and/or encephalopathy, disease duration <26 weeks, and absence of underlying cirrhosis - Other organ failure due to DILI
4	Fatal/Transplantation	Death or liver transplantation due to DILI

ALP: alkaline phosphatase, ALT: alanine aminotransferase, INR: international normalised ratio, TBL: total bilirubin, ULN: upper limit of normal.

Statistical analysis

Data are presented as mean ± SD and number (percentages) for continuous and categorical variables. The McNemar test was used to understand whether a significant difference between HI and mortality rates was found according to different definitions. Using the odds ratio and the proportion expected to change as a result of the intervention, a two-tailed, 2.0 effect size at an of 0.05 and 90% power and 20% of the population changing as a result of the different definition, 460 participants would be needed to detect

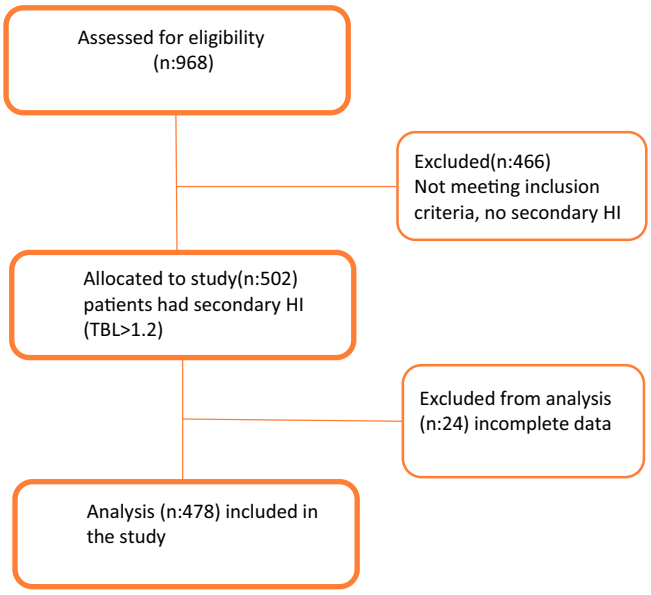

Figure 1 Flowchart.

the effect.[18] Logistic regression analysis was used to assess the influence of HI on hospital mortality: variables associated with a $p < 0.15$ in univariate analysis were entered into a stepwise regression. All tests were two-sided; $p < 0.05$ was considered for statistical significance. Sensitivity and specificity, positive (PPV) and negative predictive values (NPV), and accuracy of the definitions were also calculated for each definition, taking SOFA-1.2 as the gold standard. Inter-definition agreement and correlations were evaluated using Kappa analysis and Pearson correlation analysis.

Results

Patients

968 patients were screened for the study; 502 had secondary HI, and 24 patients were excluded due to incomplete data (Fig. 1). Four hundred seventy-eight patients were included in the investigation. The characteristics of the study population are given in Table 1. Maximum levels of AST, ALT, ALP, and GGT measured at the most severe time of the disease were as follows: AST (416 ± 1160 U/L), ALT (256 ± 746U/L), ALP (205 ± 280 U/L), GGT (140 ± 193 U/L), and TBL (1.5 ± 2.49 mg/dl).

The distribution of the number of patients according to the severity of the HI and whether the HI is hepatocellular, cholestatic, or mixed pattern can be seen in Table 2. Most of the patients had borderline and mild HI during the ICU admission and the most severe period of the disease. Moderate to severe HI developed in only 30% of the patients. The most common type of damage was the cholestatic pattern.

In this study, TBL > 1.2 mg/dL level, among the criteria defined in the SOFA score, was evaluated as the gold standard for the definition of HI. Compared to all other definitions, the SOFA TBL > 1.2 mg/dL definition was taken as the gold standard because the incidence and mortality rate values were more acceptable.

Table 1 Characteristics of the patients (n:478).

	Mean ± SD or (%)
Age, years	70 ± 15
Gender	
Female, n (%)	213 (45%)
APACHE-II Score	20 ± 8
SOFA Score on Admission	4 ± 3
SOFA Score during HI	6 ± 3
Presence of AKI on admission, n (%)	238 (50)
Requirement of Mechanical ventilation	
Non-Invasive, n (%)	194 (40)
Invasive, n (%)	98 (20)
Comorbidities, n (%)	
Hypertension	271 (57)
COPD	195 (41)
Heart failure	176 (37)
Diabetes mellitus	153 (32)
Chronic respiratory failure	146 (30)
Atherosclerotic heart disease	135 (28)
Malignancies	78 (16)
Cause of ICU admission, n (%)	
Pneumonia	100 (21)
Respiratory failure	86 (18)
COPD exacerbation	84 (17)
Pulmonary thromboembolism	42 (9)
Aspiration pneumonia	38 (8)
Cardiogenic pulmonary edema	37 (8)
Sepsis	122 (26)
Trauma	3 (0.6)
Others	66 (14)
ICU Mortality, n(%)	95 (20%)

ICU: Intensive care unit, n: number, HI: Hepatic injury, DILI: Drug-induced liver injury, BMI: Body mass index, APACHE-II: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment, TPN: Total parenteral nutrition, AKI: Acute Kidney injury, COPD: Chronic obstructive pulmonary disease.

Fig. 2 and Table 3 show HI's incidence and mortality rates according to different definitions. According to the definitions, incidence rates ranged from 10% to 45%, while mortality rates ranged from 33% to 57% (except for the SOFA-6 and SOFA-12 definitions).

Relationship between HI definition and mortality

Table 3 also shows the relationship between the definition of HI and mortality. In univariate analysis, HI was associated with hospital mortality. Variables selected for the multivariate logistic regression model included APACHE II score, HI for all definitions, presence of ICU-acquired infections, chemotherapy, mechanical ventilation, and acute kidney injury. At the end of the logistic regression analysis, when HI was defined according to ACG1, ACG2, and EASL definitions, it was found to be an independent risk factor for mortality along with the presence of APACHE II (OR:1.085, CI 95%:1.035–1.137, p:0.001), chemotherapy (OR:4.124, CI 95%:1.284–13.244, p:0.017), mechanical ventilation (OR:6.285, CI 95%:3.055–12.930, p:0.005). ICU infections (OR:1.538, CI 95%: 0.745–3.179, p:0.245) and acute kidney

Table 2 Stages of hepatic injury according to ACG and EASL definitions and type of damage according to RUCAM classification.

Patients with HI, ASG1, n:217 (45%)		
	The baseline stage of HI	Maximum stage of HI
Borderline	125 (58%)	77 (35%)
Mild	58 (27%)	78 (36%)
Moderate	14 (6%)	32 (15%)
Severe	20 (9%)	30 (14%)
Massive	-	-
RUCAM		
Hepatocelluler pattern	28 (13%)	35 (16%)
Cholestatic pattern	143(66%)	123 (57%)
Mix pattern	46 (21%)	59 (27%)
Patients with HI, EASL, n:88 (18%)		
	The baseline stage of HI	Maximum stage of HI
Stage 1	64 (73%)	52 (59%)
Stage 2	5 (6%)	6 (7%)
Stage 3	19 (21%)	29 (33%)
Stage 4	-	1 (1%)
RUCAM		
Hepatocelluler pattern	26 (29%)	26 (29%)
Cholestatic pattern	57 (65%)	58 (66%)
Mix pattern	5 (6%)	4 (5%)

ACG: American College of Gastroenterology; EASL: European Association for the Study of the Liver: DILI, RUCAM: Roussel Uclaf Causality Assessment Method.

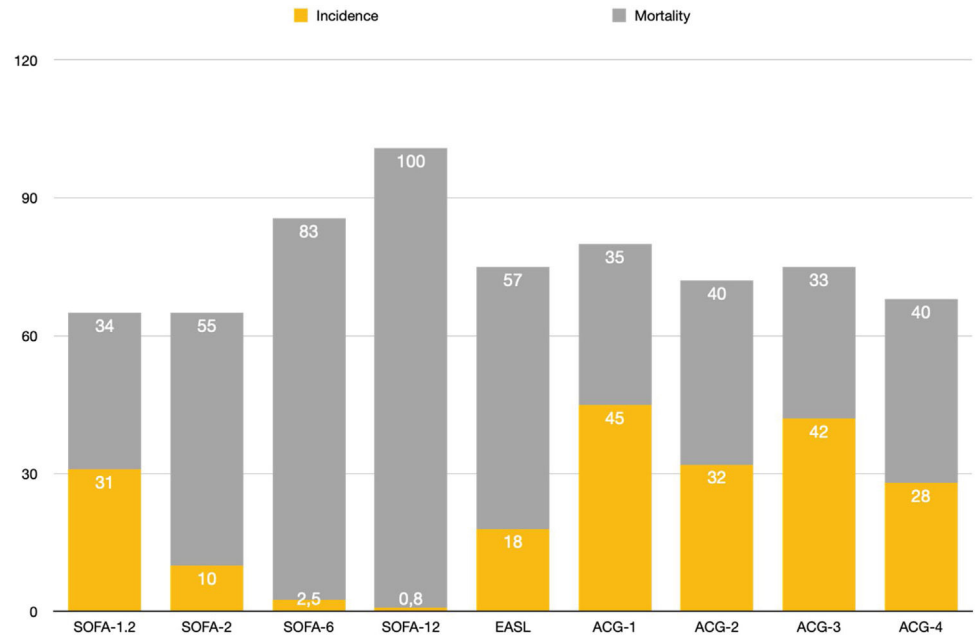

Figure 2 Incidence and mortality rates according to definitions.
SOFA-1.2,2,6,12: SOFA TBL > 1.2,2,6,12. TBL:Total biluribin, ACG:American College of Gastroenterology, EASL: European Association for the Study of the Liver.

injury (OR:0.776, CI 95%: 0.380–1.586, p:0.487) were not significant risk factors for the mortality.

Table 4 shows the sensitivity, specificity, ppv, npv, and accuracy values of the other definitions compared with SOFA-1.2 mg/dL (taken as the gold standard). Compared to the gold standard SOFA-1.2, the HI definitions with the highest sensitivity, specificity, PPV, NPV, and accuracy values were ACG-1 and ACG-3, while only ACG-1 was an indepen-

Table 3 Incidence and mortality rates and Logistic regression analysis results for the mortality of the patients according to HI definitions.

Definition	Incidence	Mortality	p	OR (95%CI) for mortality	p
ACG1	217/478 (45%)	75/217 (35%)	0.005	4.670(1.621–13.458)	0.004
ACG2	151/478 (32%)	61/151 (40%)	0.005	2.39(1.094–5.221)	0.029
ACG3	200/478 (42%)	66/200 (33%)	0.005	0.872(.390–1.950)	0.739
ACG4	133/478 (28%)	53/133 (40%)	0.005	0.896(.441–.1820)	0.762
EASL	88/478 (18%)	50/88 (57%)	0.005	3.661(1.794–7.469)	0.005
SOFA-1.2	149/478 (31%)	51/149 (34%)	0.005	1.510(0.707–3.224)	0.287
SOFA-2	49/478 (10%)	27/49 (55%)	0.005	2.061(0.653–6.507)	0.218
SOFA-6	12/478 (2.5%)	10/12 (83%)	0.005	*	
SOFA-12	4/478 (0.8%)	4/4 (100%)	0.005	*	

ACG1-4: Modified definition of HI of American Collage of Gastroenterology.
EASL: European Association for the Study of the Liver.
SOFA-1,2-2-6-12: SOFA TBL > 1.2-2-6-12 mg/dL.
* Logistic regression analysis could not be performed due to insufficient number of patients.

Table 4 Diagnostic value of definitions compared to the gold standart.

SOFA-1.2 (Gold standart)									
	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	p	Pearson correlation	p
ACG 1	99%	79%	68%	100%	85%	.630	0.005	.729	0.005
ACG 2	55%	79%	54%	80%	72%	.870	0.005	.342	0.005
ACG 3	99%	84%	74%	100%	89%	.187	0.005	.784	0.005
ACG 4	54%	84%	61%	80%	57%	.082	0.077	.399	0.005
EASL	71%	92%	71%	78%	76%	.106	0.020	.403	0.005

PPV: Positive predictive value; NPV: Negative predictive value; TBL: Total bilirubin.

dent risk factor for mortality. EASL definition was also an independent risk factor for mortality but had lower sensitivity, npv, accuracy, agreement and correlation values (Table 4).

Discussion

In this study, we found that the incidence of HI was between 10 and 45% according to the definition used, and the mortality rate was between 33% and 57% (except SOFA-6 and SOFA12 criteria). The majority of the patients had borderline or mild HI, with more than 60% presenting as a cholestatic pattern. When SOFA-1.2 was accepted as the gold standard, HI, defined according to ACG-1, ACG-2 and EASL definitions, was an independent risk factor for mortality. At the same time, ACG-1 had the highest sensitivity, specificity, ppv, npv, accuracy, agreement and correlation values. Considering ACG1 for the definition of HI, although it had a similar mortality rate to the gold standard definition, it was an independent risk factor for mortality and showed higher incidence rates. As a result, the definition with the highest diagnostic value compared to the gold standard and best predicts mortality is ALT AST elevation < 2xULN and TBL > 1.2 mg/dL. That is, adding TBL > 1.2 to the borderline criteria of ACG. This definition includes more patients with HI with the same mortality rate as the gold standard definition and supports the study results, showing that even a tiny increase in ALT and AST increases mortality.[19,20]

No specific study compares secondary HI incidence and mortality rates according to the definition in the same ICU patient population in the literature. There is no consensus on the definition of HI used in critical care patients, neither the criteria included in the definition nor their cutoff points. Since liver dysfunction is an important prognostic marker in ICU patients, bilirubin levels are included in most scoring systems, such as SOFA and SAPS. In critically ill patients without underlying liver disease, hepatic dysfunction is a predictor of ICU and hospital mortality independent of the severity of illness at presentation.

In this study, SOFA-1.2 was accepted as the gold standard test for diagnosing HI because it was part of an intensive care scoring system and had reasonable incidence and mortality rates. The SOFA score uses TBL to evaluate HI and scores from TBL > 1.2 mg/dL. The most commonly used threshold value in the literature is TBL > 2 m/dL.[11] In our study, when HI was defined as TBL > 2 mg/dL, the incidence was very low, and mortality was high. Therefore, we chose TBL > 1.2 mg/dL as the gold standard threshold value. While survival rates worsen with higher bilirubin levels, the peak time of bilirubin is later; it may increase during hemolysis and is elevated in only one-third of patients with hypoxic liver injury. So, it might not be a reliable marker alone.[8,21–23]

The ACG definition includes AST, ALT, ALP, and TBL (without any cut-off value in the original definition) criteria and lower cutoff levels. In contrast, the EASL definition has AST, ALP and TBL parameters and recommends higher cut-off values. We preferred to compare these three definitions

because we wanted to compare definitions containing different parameters and threshold points and because they are the definitions of important institutions in this regard. In our study, more than 60% of the patients had cholestatic HI. Since almost 40% of the patients have hepatocellular and mixed patterns, it suggests that the standard definition to be used in ICU should include both transaminases and cholestasis indicators. While SOFA, one of the criteria used in our study, was a scoring system related to ICU, the others (ACG, EASL) were not developed for ICU patients. On the other hand, it is well known that the smallest increase in injury markers (AST, ALT) correlates very well with mortality.[19,20] For this reason, we wanted to investigate a lower cut of values in our study. When choosing parameters, the definition of the cutoff point may also change incidence. Some researchers defined HI as any increase in liver enzymes above the ULN, while others described it as an increase at least two or three times above the ULN.[24–29] To see this effect on ICU patients, we evaluated the ACG definition as ACG-1, ACG-2, ACG-3 and ACG-4.

Another chaotic issue related to this problem is that previous studies frequently used the definition of cholestasis for the definition of HI. Currently, there is no uniform definition of cholestasis in critically ill patients. While the most commonly used and recommended by the guidelines (ACG, EASL) is the RUCAM classification, many studies used total bilirubin levels greater than 2 mg/dL criteria or 2-fold to 3-fold elevation of ALP and/or GGT to define cholestasis.[30–32] In the literature, the incidence of cholestatic liver injury in ICU patients varies between 11–36%, and mortality has been reported between 27–48%.[18,21]

Although ALP and AST are considered to indicate hepatocellular damage, ALP, TBL, and GGT are accepted as cholestasis markers; on the other hand, any of these substances may increase in any HI type. Meanwhile, although ALP, GGT, and TBL have high sensitivity for the diagnosis of cholestasis, their specificity is low as they can be elevated in many other conditions. For example, ALP may be of bone and leukocyte origin, while TBL may be elevated by non-hepatic causes like hemolysis.[33]

When the EASL definition is used in our study, it is seen that the incidence of HI was lower, and the mortality was high. The likely reasons for this are as follows: The definition of EASL was developed especially for diagnosing DILI, and this definition uses ALT, ALP, and TBL criteria.

Although most of the patients in our study group had borderline and mild HI, the emergence of HI as an independent risk factor that increased mortality by four times suggested that a more sensitive diagnosis should be used for ICU patients.

In our study group, HI developed in 29% of the patients after ICU admission. Similar to our study's results, HI rates detected during hospital admission increase during hospitalisation studies published on this subject in the literature.[25,26,34]

Having a clear and consistent definition is essential for several reasons. It allows us to evaluate how interventions impact injury incidence and mortality rates. It ensures that injury cases are reported consistently across healthcare institutions and research studies. This consistency is beneficial for healthcare planning and resource allocation purposes. Moreover, a standardised definition of injury is crucial for quality improvement efforts within healthcare institutions. Furthermore, medical societies and organisations can develop guidelines and recommendations for managing injury based on this standardised definition. On the other hand, the sensitivity and specificity of the definition greatly influence the accuracy of disease incidence. A more sensitive definition may include milder injury cases and increasing reported incidence. On the contrary, a specific definition may only identify severe cases leading to a lower reported incidence but potentially higher mortality risk. It's important to emphasise that any definition changes should be based on clinical evidence to ensure accurate diagnosis and improved patient care.

Limitations of the study

The most important limitation of our study is that it is single-centre and retrospective. The definitions we used in the comparison were not those developed for ICU patients and secondary HI, except for SOFA. Still, we used these definitions first to see how AST, ALT, ALP, and GGT affect the incidence and mortality rates, and second, they are the definitions recommended by gastroenterology associations.

Conclusion

These results showed that defining HI with only TBL may cause lower incidence and higher mortality rates, and adding other hepatic injury markers may improve the diagnostic value of the definition in ICU patients. According to this study's results, the potential best definition would be ALT AST elevation < 2xULN and TBL > 1.2 mg/dL. Further studies are necessary to validate these results.

Author's contribution

Gül Gürsel: Conceptualization, methodology, formal analysis, writing-review editing.

Ayshan Mammadova: Data curation, investigation, project administration, supervision.

Eda Macit Aydın: Visualization, project administration, supervision.

Zeynep Çınar: Project administration, supervision.

Nurgül Naurzvai. Data curation, investigation.

Sümeyye Kodalak: Data curation, investigation.

Conflicts of interest and source of funding

None were declared.

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