VALUE OF OUTCOME PROGNOSTIC SCORES OF DECOMPENSATED CIRRHOSIS IN ICU

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Abstract

Background: Liver injury that leads to necro inflammation and fibrogenesis causes cirrhosis. Histologically this disease is characterized by diffuse nodular regeneration surrounded by dense fibrotic septae, so parenchymal extinction and collapse of liver structure occur together causing pronounced distortion of hepatic vascular architecture. Patients with cirrhosis in the ICU benefit from a team approach of clinicians with expertise in both hepatology and critical care. The goals of treatment are to prevent further deterioration in liver function, reverse precipitating factors, and support failing organs. Liver transplantation is required in selected patients to improve survival and quality of life. Several ICU and liver-specific scores have been used to predict outcomes of critically ill patients with cirrhosis. Most of the studies tended to establish predictive models using prognostic scores to explore the 30-day outcomes of patients. The increased effectiveness of supportive treatments and the spread of liver transplantation programs have improved the prognosis of these patients. Child–Turcotte–Pugh (CTP) is widely applied in predicting the 1-year survival rate in patients with cirrhosis. The Mayo End-Stage Liver Disease (MELD) score has been validated in determining the severity of liver dysfunction, 3-month mortality, and the suitability for liver transplantation. The Chronic Liver Failure Consortium—Acute-on-Chronic Liver Failure (CLIF-C ACLF) score has been introduced recently and found to be superior to CTP and MELD scores in predicting short-term (28-day) mortality as well as medium-term (90-day) mortality in both ICU patients and those who were admitted in the ward.

Keywords: prognostic scores, decompensated cirrhosis, ICU

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Introduction

Liver injury that leads to necro inflammation and fibrogenesis causes cirrhosis. Histologically this disease is characterized by diffuse nodular regeneration surrounded by dense fibrotic septae, so parenchymal extinction and collapse of liver structure occur together causing pronounced distortion of hepatic vascular architecture (**1).**

Epidemiology :

Approximately 2 millions deaths per year were caused due to liver diseases. Complications of liver cirrhosis may account for 1 million deaths and others are caused by viral hepatitis and hepatocellular carcinoma. liver cirrhosis is the most common cause of the death currently worldwide.(**2**).

Most of the studies tended to establish predictive models using prognostic scores to explore the 30-day outcomes of patients**.** Jacqueline et al conducted North American Consortium for the Study of End-Stage Liver Disease- Acute-on-Chronic Liver Failure Score to assess mortality risk in hospitalized cirrhotic patients. Multivariable modelling demonstrated that this score was an independently validated tool to predict 30-day survival in cirrhotic patients. The sensitivity and specificity were 84% and 70%, respectively. Huang and Yao established a new predictive model with combination of ascites albumin, neutrophil to lymphocyte ratio, and MELD. Through logistic multivariate regression analysis, ascites albumin, neutrophil to lymphocyte ratio, and MELD were identified as the 3 independent risk factors related to the 30-day death of patients with liver cirrhosis and bacterial ascites. The AUC of this new scoring model is 0.874. Logistic regression model has certain requirements for sample size, which theoretically requires a large sample, otherwise the test formula is unreasonable. Furthermore, logistic regression model cannot solve the problem of multicollinearity. As far as we know, there is rarely study using random forest model to predict the death of cirrhotic patients within 30 days of admission up to now. **(3)**

The role of SAPS II and SOFA in predicting hospital mortality of ICU patients has been reported in numerous studies. Dupont et al conducted a retrospective study to assess the predictive abilities of different prognostic scores, and results revealed the superiority of SOFA and Model for End-Stage Liver Disease (MELD) score compared to other prognostic scores for mortality prediction in ICU patients hospitalized with a diagnosis of cirrhosis. SOFA was considered as the best prognostic score to evaluate cirrhotic patients in the ICU according to nearly all of the literature**.** Our study also identified SOFA as an important predictor for death, and SAPS II presented better discriminative ability for death of cirrhotic patients within 30-day hospitalization. A prior prospective study reached a conclusion that SAPA II and SOFA showed better prediction performance than MELD in ICU mortality for cirrhotic patients. In the future, larger sample sizes are needed to verify the priorities of different prognostic scoring systems in ICU cirrhotic patients. **(3)**

Additionally, elevated BUN and bilirubin were found to be independently correlated with hospital mortality**.** Ning et al discussed the clinical features and prognosis in Chinese cirrhotic patients with ascites, and found the concentration of BUN was an independent risk factor for 30-day hospital mortality. The serum bilirubin level better reflects the liver's synthetic and excretory functions, thus, the mass of prognostic scoring systems included TBIL and bilirubin as ingredients**.** Our study demonstrated that BUN, TBIL and bilirubin were significant predictors for 30-day admission death. Previous studies provided a specific explanation**.** It is reported that intrahepatic cholestasis, portal flow distortion or shunting, and hemolysis caused by splenomegaly may all lead to the increased level of bilirubin. Recent research compared the value of bilirubin and TBIL for predicting prognosis of cirrhotic patients, and results showed bilirubin performed better predictive value. **(4)**

The increased effectiveness of supportive treatments and the spread of liver transplantation programs have improved the prognosis of these patients Nonetheless, the prognosis of cirrhotic patients admitted to the ICU remains poor , especially among those admitted to the general ICU who are ineligible for transplantation. The prognosis is determined by the extent of hepatic and extrahepatic organ dysfunction. The occurrence of three or more organ failures in cirrhotic patients has an almost certain fatal outcome. **(5)**

Reductions in CLD mortality rates vary across regions and reflect country-specific approaches to viral hepatitis prevention and treatment, as well as trends in IVDU, alcohol consumption, and obesity rates. From 1980 to 2010, mortality significantly declined in countries as varied as China (66% AADR reduction from 43 to 16 per 100,000) and the United States (24% reduction from 15 to 11 per 100,000), largely because of HBV prevention efforts. Meanwhile, other countries have experienced significant mortality reductions but still face persistently high liver disease mortality

rates: an example is Egypt with a 26% AADR decline from 98 to 72 per 100,000 largely a result of massive efforts targeting chronic hepatitis C infection and schistosomiasis. Finally, there are regions that have experienced increases in mortality rates. For example, AADR increased by 24% in Mongolia (44-55 per 100,000) and by 18% in India (17-20 per 100,000), largely driven by viral hepatitis and in part by increasing alcohol consumption and obesity rates; AADR increased by 64% in Russia (11-19 per 100,000) and 31% in the United Kingdom (7-9 per 100,000) largely because of alcohol-related liver disease. **(6)**

Marked improvements in survival have been noted in patients with acute decompensation (AD) of cirrhosis and organ failure admitted to specialist liver transplant (LT) centres over the last decade. This improvement can partly be explained by reductions in admission organ failure scores as patients were admitted earlier during their critical illness. In cohorts from the Royal Free Hospital, London and King's College Hospital, London the aetiology of underlying cirrhosis was not associated with a survival difference. Furthermore, patients admitted following gastrointestinal haemorrhage had lower mortality rates compared to those with multi-organ failure. Patients with cirrhosis and significant acute organ dysfunctions have recently been classified by international consensus as suffering from the distinct clinical entity of acute-on-chronic liver failure (ACLF) **(7)** .

Value of outcome prognostic scores of decompensated cirrhosis in ICU

1. Child Pugh score

Definition :

The Child-Pugh scoring system (also known as the Child-Pugh-Turcotte score) was designed to predict mortality in cirrhosis patients. Originally conceptualized by Child and Turcotte in 1964 to guide the selection of patients who would benefit from elective surgery for portal decompression, it broke down patients into three categories: A – good hepatic function, B – moderately impaired hepatic function, and C – advanced hepatic dysfunction. Their original scoring system used five clinical and laboratory criteria to categorize patients: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status. The scoring system was modified later by Pugh et al., substituting prothrombin time for clinical nutrition status. Additionally, they introduced variable points for each criterion based on increasing severity **(8)**:

Measure		1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)		< 34 (< 2)	34–50 (2–3)	> 50 (> 3)
Serum albumin, g/dL		> 3.5	2.8–3.5	< 2.8
OR	Prothrombin time, prolongation (s)	< 4.0	4.0–6.0	> 6.0
	INR	< 1.7	1.7–2.3	> 2.3
Ascites		None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy		None	Grade I–II	Grade III–IV

The severity of cirrhosis:

Points	Class	One-year survival	Two-year survival
5–6	A	100%	85%
7–9	B	80%	60%
10–15	C	45%	35%

Issues of Concern

Historically the Child-Pugh classification was used for liver transplant allocations. However, there were three primary limitations to its use: 1) grading ascites and encephalopathy require a subjective assessment, 2) the classification system does not account for renal function, and 3) there are only ten different scores (based on points) available. This last limitation was significant because patients were not able to be adequately differentiated based on the severity of the disease, and therefore wait time had a considerable impact on prioritization. Practically speaking, a patient with an INR of 6 and bilirubin of 14 could potentially have the same Child-Pugh score as a patient with an INR of 2.3 and bilirubin of 4.0. The MELD score, which has a broader range of more continuous variable values, was created to account for these differences. The original MELD score calculation used the patient's bilirubin level, creatinine level, INR, and cause of liver disease. **(8)** Since then, it has evolved to exclude causes of disease and takes into account the serum sodium level and whether the patient is on dialysis.

Clinical Significance

The Child-Pugh score has been validated as a predictor of postoperative mortality after portocaval shunt surgery and predicts mortality risk associated with other major operations. After abdominal surgery, Child class A patients have a 10% mortality rate; Child class B patients have a 30% mortality rate, and Child class C patients have

a 70 to 80% mortality rate Child class A patients are generally considered safe candidates for elective surgery. Child class B patients can proceed with surgery after medical optimization but still have increased risk. Elective surgery is contraindicated in Child class C patients. The Child-Pugh score can help predict all-cause mortality risk and development of other complications from liver dysfunction, such as variceal bleeding, as well. In one study, overall mortality for these patients at one year was 0% for Child class A, 20% for Child class B, and 55% for Child class C.**(7)**

Evaluation :
Despite involving numerous subjective parameters and its limited scope of definition, CTP is still the most commonly used scoring system in the determination of prognosis in cirrhotic patients. In one such study by Botta, et al., 1-year mortality rates of patients with CTP A, B and C were 12, 25 and 44%, respectively. Ho, et al. Reported on mortality rates of 20, 41.9 and 81.6% in ascending order of CTP class. Similar findings were also reported by Wehler, et al.6 Furthermore, a metaanalysis on 118 studies clearly established that higher CTP scores and the presence of more complications were associated with higher mortality rates.**(8)**
On the other hand, some investigators have suggested that the CTP score had many short-comings when used to determine post-operative mortality in cirrhotic patients. This has been attributed to the use of subjective parameters such as the presence of ascites and encephalopathy as well as it being deficient with regard to other conditions that may be encountered in ICU patients, unrelated to cirrhosis.Although CTP scores may correctly indicate severity of disease, CTP remains a poor prognostic model in cirrhotic patients with multiorgan failure as well as a poor predictor of mortality. .**(9)**

2. Glasgow coma scale :
The Glasgow Coma Scale (GCS) is a clinical scale used to reliably measure a person's level of consciousness after a brain injury. **(10)**

The GCS assesses a person based on their ability to perform eye movements, speak, and move their body. These three behaviours make up the three elements of the scale: eye, verbal, and motor. A person's GCS score can range from 3 (completely unresponsive) to 15 (responsive). This score is used to guide immediate medical care after a brain injury (such as a car accident) and also to monitor hospitalised patients and track their level of consciousness.
Lower GCS scores are correlated with higher risk of death. However, the GCS score alone should not be used on its own to predict the outcome for an individual person with brain injury.

Scoring :
The Glasgow Coma Scale is used for people above the age of two and composed of three tests: eye, verbal, and motor responses. The scores for each of these tests are indicated in the table below.
Glasgow Coma Scale **(10)**

Glasgow Coma Scale							
Test	**Not Testable (NT): Examples**	**1**	**2**	**3**	**4**	**5**	**6**
Eye (ocular response)	**Severe trauma to the eyes, enucleation**	**Does not open eyes**	**Opens eyes in response to pain**	**Opens eyes in response to voice**	**Opens eyes spontaneously**	**N/A**	**N/A**
Verbal (oral response)	**Intubation, non-oral language disability, linguistic barrier**	**Makes no sounds**	**Incomprehensible sounds**	**Inappropriate words**	**Confused and disoriented, but able to answer questions**	**Oriented to time, person, and place, converses normally**	N/A
Motor (motoric response)	**Paralysis/hemiparesis (acquired causes such as post-stroke, post-neurological injury; congenital/innate such as cerebral palsy)**	**Makes no movements**	**Abnormal extension (decerebrate posture)[b]**	**Abnormal flexion (decorticate posture)**	**Flexion / Withdrawal from painful stimuli**	**Moves to localise pain**	Obeys command

The Glasgow Coma Scale is reported as the combined score (which ranges from 3 to 15) and the score of each test (E for eye, V for Verbal, and M for Motor). For each test, the value should be based on the best response that the person being examined can provide. **(Glynn 2012)**

Interpretation :
Individual elements as well as the sum of the score are important. Hence, the score is expressed in the form "GCS 9 = E2 V4 M3 at 07:35". Patients with scores of 3 to 8 are usually considered to be in a coma. **(10)** Generally, brain injury is classified as:
Severe, GCS ≤ 8
Moderate, GCS 9–12
Minor, GCS ≥ 13. **(10)**

Clinical Significance :
Assessment of responsiveness with the Glasgow Coma Scale is widely used to guide early

management of patients with a head injury or other kind of acute brain injury. Decisions in more severely impaired patients include emergent management such as securing the airway and triage to determine patient transfer. Decisions in less severely impaired patients include the need for neuroimaging, admission for observation or discharge. Serial Glasgow Coma Scale assessments are also critical in monitoring the clinical course of a patient and guiding changes in management. **(10)**

The information gained from the three components of the Scale varies across the spectrum of responsiveness. Changes in motor response are the predominant factor in more severely impaired patients, whereas eye and verbal are more useful in lesser degrees. In individual patients, the clinical findings in three components should, therefore, be reported separately. The total score communicates a useful summary overall index but with some loss of information. **(10)**

Jain S, Iverson LM. Glasgow Coma Scale. [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls

Relation to Outcome :

A relationship between assessments of the GCS (typically reported as the total GCS Score) and the outcome was shown clearly by Gennarelli et al., who demonstrated the existence of a continuous, progressive association between increasing mortality after a head injury and decreases in GCS Score from 15 to 3. This association has been seen in many other subsequent studies. The findings for the eye, verbal and motor responses also relate to the outcome but in distinctive ways so that assessment of each separately yields more information than the aggregate total score. **(8)**

However, although it is one of the most powerful clinical prognostic features, neither the GCS score nor any single feature alone should be used to predict an individual patient's outcome. This is because the prognostic implications of the score are influenced by several factors. These include the diagnosis, and in trauma the cause and if there are extracranial injuries, patient-related factors such as age and other clinical indices (such as pupillary dysfunction and imaging findings), the GCS score is a key component of multifactorial models for prediction of outcomes such as in the IMPACT and CRASH trials. **(11)**

3. MELD score :

History :

MELD was originally developed at the Mayo Clinic by Dr. Patrick Kamath, and at that point was called the "Mayo End-stage Liver Disease" score. It was derived in a series of patients undergoing TIPS procedures. The original version also included a variable based on the underlying etiology (cause) of the liver disease. The score turned out to be predictive of prognosis in chronic liver disease in general, and—with some modifications—came to be applied as an objective tool in assigning need for a liver transplant. The etiology turned out to be relatively unimportant, and was also regarded as relatively subjective; it was therefore removed from the score. **(11)**

The successor of MELD, an advanced scoring system, made by collaboration between Massachusetts General Hospital and IBM, called MELD-Plus was introduced in 2017. **(11)**

Definition :

The **Model for End-Stage Liver Disease**, or **MELD**, is a scoring system for assessing the severity of chronic liver disease. It was initially developed to predict mortality within three months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt (TIPS) procedure, and was subsequently found to be useful in determining prognosis and prioritizing for receipt of a liver transplant. **(11)**. This score is now used by the United Network for Organ Sharing (UNOS) and Eurotransplant for prioritizing allocation of liver transplants instead of the older Child-Pugh score. **(11)** .

Determination :

MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. It is calculated according to the following formula: **(11)**:

MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43MELD scores are reported as whole numbers, so the result of the equation above is rounded. UNOS has made the following modifications to the score: **(11)**:

If the patient has been dialyzed twice within the last 7 days, then the value of serum creatinine should be 4.0 mg/dL Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8 a value of 1.0 is used) to prevent subtraction from any of the three factors, since the natural logarithm of a positive number below 1 (greater than 0 and less than 1) yields a negative value.

The etiology of liver disease was subsequently removed from the model because it posed difficulties such as how to categorize patients with multiple causes of liver disease. Modification of

the MELD score by excluding etiology of liver disease did not significantly affect the model's accuracy in predicting three-month survival.
Patients with a diagnosis of liver cancer will be assigned a MELD score based on how advanced the cancer is.

Interpretation :
In interpreting the MELD Score in hospitalized patients, the 3 month observed mortality (considering 3,437 adult liver transplant candidates with chronic liver disease who were added to the OPTN waiting list at 2A or 2B status between November, 1999, and December, 2001) is: **(12)**:

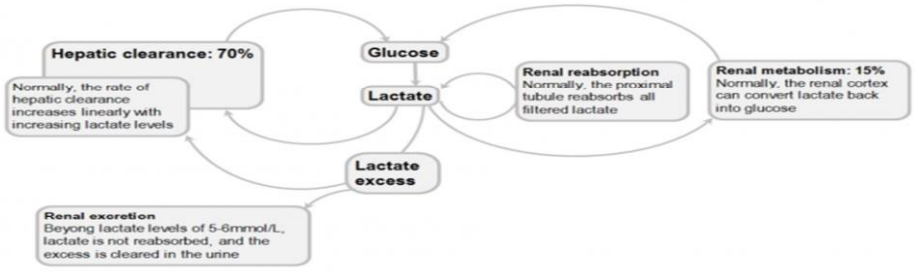
MELD score	Percentage mortality
40 or more	**71.3%[6]**
30–39	**52.6%[6]**
20–29	**19.6%[6]**
10–19	**6.0%[6]**
9 or less	**1.9%[6]**

Applications of MELD score include:
The best outcomes with TIPS occur among patients with a MELD score less than 14.
Patients with MELD scores greater than 24 who are reasonable liver transplant candidates are probably best served by foregoing TIPS placement.
MELD Na
Sodium (Na) is incorporated into MELD calculation to improve the predicitivity MELD score. Formula of MELD Na was calculated as: **MELD- Na=** MELD**+1.32 X(137- Na) – [0.033 X MELD*(137- Na]. (13).**
MELD Lactate score
Recent studies showed that MELD- Lactate (MELD- LA) performs significantly a better predicting factor of inpatient mortality compared with MELD in Iiver cirrhosis.**(13).**
MELD- Lactate is calculated using the formula [**5.68 X Loge(lactate)+0.64 X (original MELD)+2.68].** MELD Lactate can provide better predicting factor for patient outcomes more than MELD sodium and original MELD. **(14)**

Blood Lactate :
- **Lactate production:**

Tissue hypoperfusion conditions are the cause of increased lactate in the blood. Blood lactate level directly correlates with the patient's risk of deathStudies shows that lactate elevation in sepsis may due to stimulation of beta-2 receptors by endogenous epinephrine. Adrenergic stimulation up regulates glycolysis, producing more pyruvate leading to more lactate that occur in Tricyclic Acetic cycle (TCA cycle) or in Krebs cycle in the cell's mitochondria. This is an entirely aerobic process. **(15)**.
Lactate production occurs because the TCA cycle is not able to keep up with the rapid rate of glycolysis and the metabolic needs of a body in acute decompensation. Some studies show that The lungs and leukocytes may serve as additional sources of lactate , as lactate may increase if lung injury occur in the absence of tissue hypoxia. Furthermore, leukocytes, which are upregulated during sepsis, generate lactate during phagocytosis Thus, lactate is a measure of a stress response with serum catecholamines. So seizure, asthma,sepsis, exercise… all result in lactate generation **(15).**

Clearance, Excretion, and Reabsorption:
Liver, skeletal muscles,kidney, and myocardium can all consume the increased lactate so They prevent hyperlactemia during exercises or even times of Stress The rate of hepatic clearance increases directly with the production of lactate. The liver can increaseS its capacity of lactate clearance up to seven-fold. Acidosis in a septic patient increases hepatic lactate metabolism, also increases lactate uptake and utilization by the kidney. With worsening acidosis, significant liver disease, liver failure, systemic infection, and cardiovascular collapse disturb this balance. **(16).**



Lactate kinetics. Image by Deranged Physiology.

Figure (1) :

Lactate as a substrate:
The mitochondria can metabolize lactate and use it as fuel. Lactate is Considered a source of energy in multiple organs including the brain, liver, heart, kidney, and muscles. The problem arises when the oxidative system disrupts due to hypoxemia, iatrogenic causes, and drug induced causes. In these conditions, the mitochondria will generate a lactate, rather than consuming tissue.**(17).**

Beta adrenergic blocking agents:-
Multiple studies show the increase of blood lactate is multifactorial rather than only due to tissue hypoxia and tissue perfusion. One example is beta adrenergic stimulation contributing to increased generation of lactate. A study suggests that the elevation of lactate level may be blunted in a sepsis conditions using beta blockers such as metoprolol. **(18).**

Etiology of increased blood lactate level:-
Lactic acid is normally produced by the skin, brain tissues, muscles, red cells and the gastrointestinal tract. Also the skeletal muscles produce excess lactate during heavy exercise. This excess lactate is metabolized by the liver and the Kidney where it is used in gluconeogenesis. So pathologic elevation of lactate may be due to even over production that exceeds the capacity of the liver to metabolize or due to the liver impairement. Severe convulsions, Grand Mal epilepsy, produce excess lactate if there is impaired liver Functions such as cirrhosis, hypothermia, severe hypovolaemia, sepsis, severe hypotension cause lactic acidosis **(18).**

Epidemiology of lactic acidosis: -
A study show that there is association between the severity of lactic acidosis and the time needed to be corrected and the mortality rates as the high values of lactic acid and longer time to be corrected are linked to high mortality rates. As this study found by prospective analysis that 6% of studied 2550 patients show severe lactic acidosis. And 83 %.of those patients with severe lactic acidosis were treated with vasopressors and pH of 6.8:7.2 showing 57% mortality rate.**(4).**
Severe lactic acidosis(pH <7.2) may be comorbid with shock and this is often associated with high mortality rate(about 50 %) and it may be no survival rates if PH less than 7.**(19)**

Pathophysiology: -
Lactate level normally in unstressed patients is less than 2 mmol /L .**(19)**
When blood lactate level is increased above2 mmol/ L, but less than 5mmol/L and without metabolic acidosis,it is defined as hyperlactatemia. Whereas lactic acidosis is characterized by persistent blood lactate level more than 5 mmoI/L in presence of metabolic acidosis. **(19)**
Lactic acidosis reduce cardiac contractility and decrease vascular response to vasopressor **(11).**
Also Iactic acidosis worse other comorbidities and increase risk of mortality rate independently on organ failure and shock.**(11).**

A study classifyed lactic acidosis into 2 categories: type A that occurs in cases of tissue hypoperfusion or poor oxygenation; and type B that occurs in absence of hypoperfusion or poor oxygenation of tissues. Examples of type A Iactic acidosis include all shock diseases(e.g ; cardiogenic, hypovlemic, septic ,obstructive), ischemic states, severe cases of shivering and seizures/ convulsions. Examples of type B lactic acidosis are liver disease, excessive exercise, total parenteral nutrition, HIV, mitochondrial myopathay, diabetes mellitus, thiamine deficiency, pheochromocytoma, malignancy, drugs, ethanol, cyanide, acetaminophen ,isoniazid, salicylates, methanol, and epinephrine **(20)**.

Toxicokinetics:-
According to Stewart approach to acid-base modification, lactic acid as a strong acid is dissociated completely in water at physiological pH generating hydrogen ions(H+). Increased lactate production in turn increase H+ ions generation intracellularly that extrude from cells to maintain physiological intracellular pH but decrease extracellular PH depending on the level of increased generation of lactate so lactic acidosis occur even if there is a constant value of choremia, albuminemia and PC02**(21)**

Blood lactate Level in Ill Critically Cirrhotic patients:
In splanchnic circulation in patients with acute liver failure, glycolysis is accelerated generating more lactate without splanchnic hypoxia. Cirrhotic Patients show higher blood lactate than controls, and the lactate levels increase with the cirrhosis severity. Accelerated glycolysis in the s planchnic circulation may be the cause of this increased lactate, but the decreased gluconeogenesis may be not incorporated in that A retrospective cohort study conducted between january2007 and december 2013 including 12281 patients of age above 18 years old age of suspected infection and showed that serum lactate level was higher significantly in septic patients with liver cirrhosis. Also, the sensitivity of serum lactate level for predicting themortality rates is higher in Cirrhotic

patients than others, and this trend is increasing wouith s ouith increase liver severity.**(22).**

Lactate clearance is made by many organs but mainly by liver, as the liver accounts for about 70% of lactate clearance. severe acidosis PH< 7.35 or base deficit greater than 6 is associated with blood lactate level more than5 mmol/ litre, mortality rate is high up to 80%. Lactate clearance and blood lactate level may be a good predictor of mortality rates in decompensated cirrhotic patients. This predictor is independent and can be incorporated into scoring system to improve the predicting outcome scores. This lactate predictor is quick and easy to stratify risky patients, but there is a need for further studies to verify the use of this predictor. **(22).**

Lactate as a predictor of outcome of some diseases:-

For examples:-

Tissue hypoxia and accelerated glycolysis increase level of blood lactate. So serum lactate can be a predictor of mortality rate in these cases. The Surviving Sepsis Campaign and the National Quality Forum show that lactate measurement is significantly usefulI in management of patients with sepsis Also lactate is used in risk assessment in patients with suspected or confirmed sepsis **(23)**.

Assessment of lactate value may be a predictor of 6-monthes mortality in decompensated liver cirrhosiss caused by HBV. And the accuracy of the other prognosis scores ;MELD andChild-pugh may be improved by assessment lactate level predictor on admission of patient. High lactate values are associated with high mortality -rates- in patients with trauma **(23)**.

One study, Itwas showed that there is association between high serum lactate level and in-hospital mortality and more hospital – Stay length for patients surviving to be discharged than those having normal lactate levels.

A study included 450 patients stratifying them into lactate levels:< 2 mmol/ L, 2-4 mmol/L and > 4mmol / L. This study found that group of lactate2-4 mmol/L had an in-hospital mortality rate 12% and group of Lactate > 4 mmol/L had an in-hospital mortality rate 40.7%.**(24)**.

In cases of septic shock or severe sepsis, patients with less lactate clearance needed more vasopressor support, mechanical ventilation and having higher mortality rates. A retrospective observational study performed from January2010 to December2016 including 61,151 patients, but 14,015 patients who had lactate test on arrival to Emergency Department(ED). This study show that patients with high lactate levels (>2.6 mmol/L) have significantly more mortality rates than those of low lactate levels. Serum lactate test may be an effective screening test to stratify risk patients in the ED.Additionally,serum lactate level>2.6 mmol/ L Can predict in- hospital mortality rate in 30- day in unselected patients admitted to hospitals on arrival to ED **(25)**.

A study included patients with acute gastroentestinal bleeding(GIB) show that elevated lactate values are associated with the need to transfusions, ICU admissions and endoscopies. So lactate may be a prognostic predictor in the triage of patients with acute GIB.Mortality rates in spontinuons subarachnoid haemorrhage(caused by ruptured aneurysms) can be predicted by serum lactate level. A cohort study of critically ill patients in ICU suggests mortality rates are associated Strongly to lactate values, and the patients use metformin show a lower mortality rate than the non-user metformin although the similar lactate levels of them. **(25)**.

In critically ill diabetic patients with acute myocardial infarction, High lactate levels can point to poor prognosis and increased complic- ations and risk of severe heart arrhythmias, heart Failure, Cardiogenic shock,even high mortality rate.Increased odds of severe COVID-19 disease by 6-fold was related with elevated lactate dehydrogenase, Also increased mortality odds with > 16-Fold Liu et al., a study show that the prognostic predicitivity of lactate value is independent and superior to the q SOFA but similar to that of SOFA **(26).**

Lactate level can be an independent predictor of prognosis of outcome in decompensated cirrhosis. It may have significantly discrimination ability similar to the MELD score and Child- pugh score. And the accuracy of these scores are improved by lactate adjusting. **(26).**

4. APACHE II

("Acute Physiology and Chronic Health Evaluation II") is a severity-of-disease classification system,[1] one of several ICU scoring systems. It is applied within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. The first APACHE model was presented by Knaus et al. in 1981.

Application :

APACHE II was designed to measure the severity of disease for adult patients admitted to intensive care units. It has not been validated for use in children or young people aged under 16.

This scoring system is used in many ways which include:
Some procedures or some medicine is only given to patients with a certain APACHE II score
APACHE II score can be used to describe the morbidity of a patient when comparing the outcome with other patients.
Predicted mortalities are averaged for groups of patients in order to specify the group's morbidity.

Even though newer scoring systems, such as APACHE III, have replaced APACHE II in many places, APACHE II continues to be used extensively because so much documentation is based on it.[citation needed]
The point score is calculated from 12 admission physiologic variables comprising the Acute Physiology Score, the patient's age, and chronic health status:

Physiologic Variable	Points								
	+4	+3	+2	+1	0	+1	+2	+3	+4
1. Temperature (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
2. Mean arterial pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
3. Heart rate (/min)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
4. Respiratory rate (/min)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
5. Oxygenation (mmHg) a. A-aDO_2 if FiO_2 ≥0.5 b. PaO_2 if FiO_2 <0.5	500	350-499	200-349		<200 >70	61-70		55-60	<55
6. Acid-base balance a. Arterial pH b. Serum HCO_3 (mEq/l) if no arterial blood gas	≥7.7 ≥52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15
7. Sodium (mEq/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
8. Potassium (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
9. Creatinine (mg/dl)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
10. Hematocirt (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<2.5
11. White blood count (×1000/mm^3)	≥40		20-39.9	15.19.9	3-14.9		1-2.9		<1
12. Glasgow Coma Score (GCS)	Score = 15 minus actual GCS								
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6									
C. Chronic Health Points*									
Total APACHE II Score (add together the points from A+B+C)									

* Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immune-compromised as defined below, assign points as follows:
5 points for non-operative or emergency post-operative patients
2 points for elective post-operative patinets

The score is not recalculated during the stay. It is by definition an admission score. If a patient is discharged from the ICU and subsequently readmitted, a new APACHE II score is calculated.

Evaluation:
A large number of studies have confirmed that the APACHE II score is a useful prognostic biomarker of the mortality of patients with a critical illness. A retrospective study of 200 Iranian ICU patients reported that an APACHE II score of 15 provides the best accuracy to predict the mortality of critically ill patients. This study indicated that APACHE II score of 17 is an optimal cut-off to distinguish patients with a high or low risk of mortality. The difference in results may be attributed to different sources of patients. Liu et al. have shown that the initial APACHE II scores on the day of ICU admission are correlated with the outcomes of patients **(26)**. A study that included 109 cirrhotic MICU patients reported that APACHE II could be used as a predictor of mortality. Notably, most currently available studies used APACHE II score within 24 h after admission, which is helpful in classifying patients and early identifying risk factors. However, some factors affecting the prognosis of ICU patients within 24 h may not be included in the APACHE II score system, resulting in inaccurate predictions of patients' outcomes. This study found that the first-day APACHE II score has a poor calibration on hospital mortality of the included cohort of patients. Kim et al. also found that the APACHE II of the first 24 h after admission to the ICU exhibits

poor calibration for hospital mortality in a study including 826 Korean patients. In another large-scale study including 141,106 ICU patients in the U.K., the APACHE II score showed good discrimination but imperfect calibration for hospital mortality **(25).**

The cut-off of the APACHE II scores that provides the best accuracy in predicting the mortality of patients still has controversy. It was reported that an APACHE II score of 15 gave the best accuracy to predict ICU mortality. However, another two studies reported that the best cut-off score for APACHE II in predicting hospital mortality was 13.5. **(25).**

In addition to predicting outcomes, scoring systems like APACHE II are also used to evaluate clinical performance, the standard of care in the ICU, and to compare the effectiveness of ICUs with one another. Compared to other scoring systems, APACHE II has a sensitivity of 89.9% and specificity of 97.6%; SOFA has 90.1% sensitivity and 96.6% specificity; while mNUTRIC score has 97.2% sensitivity and 74.0% specificity. However, the mortality risk is frequently overstated based on APACHE II values. This is mainly because of the lack of proper standard implementation as well as poor scoring system skills of medical workers. To mitigate these issues and improve adoption, strict clinical standards must be followed, and medical workers utilizing these scores must get frequent training, in order for the APACHE II scoring system to be used properly. **(12)**

5. The sequential organ failure assessment score (SOFA score) :
previously known as the sepsis-related organ failure assessment score, is used to track a person's status during the stay in an intensive care unit (ICU) to determine the extent of a person's organ function or rate of failure. **(22)** The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems.

Medical use :

The SOFA scoring system is useful in predicting the clinical outcomes of critically ill patients. . According to an observational study at an Intensive Care Unit (ICU) in Belgium, the mortality rate is at least 50% when the score is increased, regardless of initial score, in the first 96 hours of admission, 27% to 35% if the score remains unchanged, and less than 27% if the score is reduced. Score ranges from 0 (best) to 24 (worst) points. **(20)** .

	Central nervous system	Cardiovascular system	Respiratory system	Coagulation	Liver	Renal function
Score	Glasgow coma scale	Mean arterial pressure OR administration of vasopressors required	PaO_2/FiO_2 [mmHg (kPa)]	Platelets ($\times 10^3/\mu l$)	Bilirubin (mg/dl) [µmol/L]	Creatinine (mg/dl) [µmol/L] (or urine output)
+0	15	MAP ≥ 70 mmHg	≥ 400 (53.3)	≥ 150	< 1.2 [< 20]	< 1.2 [< 110]
+1	13–14	MAP < 70 mmHg	< 400 (53.3)	< 150	1.2–1.9 [20-32]	1.2–1.9 [110-170]
+2	10–12	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	< 300 (40)	< 100	2.0–5.9 [33-101]	2.0–3.4 [171-299]
+3	6–9	dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	< 200 (26.7) and mechanically ventilated including CPAP	< 50	6.0–11.9 [102-204]	3.5–4.9 [300-440] (or < 500 ml/day)
+4	< 6	dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min	< 100 (13.3) and mechanically ventilated including CPAP	< 20	> 12.0 [> 204]	> 5.0 [> 440] (or < 200 ml/day)

Quick SOFA score :

The Quick SOFA Score (quickSOFA or qSOFA) was introduced by the Sepsis-3 group in February 2016 as a simplified version of the SOFA Score as an initial way to identify patients at high risk for poor outcome with an infection. **(26)** . The SIRS Criteria definitions of sepsis are being replaced as they were found to possess too many limitations; the "current use of 2 or more SIRS criteria to identify sepsis was unanimously considered by the task force to be unhelpful." The qSOFA simplifies the SOFA score drastically by only including its 3 clinical criteria and by including "any altered mentation" instead of requiring a GCS <15. qSOFA can easily and quickly be repeated serially on patients.

Assessment	qSOFA score
Low blood pressure (SBP ≤ 100 mmHg)	1
High respiratory rate (≥ 22 breaths/min)	1
Altered mentation (GCS ≤ 14)	1

The score ranges from 0 to 3 points. The presence of 2 or more qSOFA points near the onset of infection was associated with a greater risk of death or prolonged intensive care unit stay. These are outcomes that are more common in infected patients who may be septic than those with uncomplicated infection. Based upon these

findings, the Third International Consensus Definitions for Sepsis recommends qSOFA as a simple prompt to identify infected patients outside the ICU who are likely to be septic. qSOFA has also been found to be poorly sensitive though decently specific for the risk of death with SIRS possibly better for screening. **(27)**.

qSOFA utility

The qSOFA was designed to be used in non-ICU settings, where the healthcare provider might not have access to all the information used in the SOFA score. Settings include the emergency department or other healthcare settings where patients are initially assessed. The three criteria used (systolic blood pressure, respiratory rate, and GCS) can be quickly gathered in the emergency department, to risk stratify patients and provide potentially ill patients with quick interventions. This scoring system is used to identify potential patients with sepsis. **(27)**.

Evaluation :

study have shown the SOFA score to be the best prognostic model, among the scoring systems studied, at predicting prognosis in cirrhotic patients admitted to the ICU. Other studies have demonstrated that the SOFA score is not only useful in grading organ dysfunction in cases with sepsis, trauma or after surgery, but that it is also the best prognostic indicator that could be used for cirrhotic patients. In a study on 160 patients with cirrhosis admitted to the ICU, Tsai, et al. Demonstrated that the SOFA score was better than the CTP score in predicting mortality. Chen, et al. Reported a mortality rate of 68.6% among 102 cirrhotic patients admitted to the ICU. They also reported the SOFA score to be an excellent predictor of prognosis in comparison to the CTP score. **(9)**

Cholongitas, et al. Compared the prognostic value of SOFA, APACHE II, MELD and CTP scores while evaluating 6-week mortality of 312 cirrhotic patients admitted to the ICU. They reported the SOFA model to be the best, and the CTP score the worst indicator. Furthermore, the MELD score was found to be superior to the APACHE scores (AUROC values for SOFA, MELD, APACHE II and CTP were 0.83, 0.81, 0.78 and 0.72, respectively). Six-week mortality rate was calculated at 65.1%.12 In yet another study, Wehler, et al. Enrolled 143 cirrhotic patients who were admitted to the ICU. They demonstrated that the SOFA score had an excellent predictive value in determining short-term prognosis, and was superior to both the APACHE II and CTP scores (AUROC values for SOFA, APACHE II and CTP were 0.94, 0.79 and 0.74, respectively). They also reported on an ICU mortality rate of 36%, overall hospital mortality rate of 46% and 6-month mortality rate of 56%. **(28)**

The SOFA score is an excellent model in that it provides an easy to apply scoring system which may be used to provide objective information to patients and their relatives regarding the prognosis of the disease, as well as helping in making clinical decisions regarding management. Despite all its merits, the SOFA score is not without its limitations. It utilizes variables from the Glasgow coma scale used to evaluate neurological dysfunction, and the subjective nature of these parameters may result in random errors of evaluation, particularly since cognitive abilities of ICU patients are frequently altered by used of sedatives and analgesics. **(28)**

6. CLIF ACLF

The CLIF-C ACLF was calculated using the following formula: CLIF-C ACLF = 10 × (0.33 × CLIF- OFs + 0.04 x Age + 0.63 × ln (WBC count)-2) [3]. Organ failure was defined according to Moreau et al.

Acute-on-chronic liver failure (ACLF) is a syndrome that develops in patients with an acute decompensation of liver cirrhosis and is characterized by development of organ failure and high short-term mortality **(7)** . The diagnostic criteria for organ failure and subsequent ACLF gradation are based on the European Foundation for the study of chronic liver failure (CLIF) organ failure score (CLIF-OF score), a modified version of the Sequential Organ Failure Assessment (SOFA) score. **(7)** . Depending on the ACLF grade, 28-day mortality ranges from 23.3% in ACLF grade 1 to 75.5% in ACLF grade 3 and most patients require intensive care and organ support. **(29)** .

In order to prognosticate mortality in patients with ACLF more accurately, the CLIF consortium derived and validated a new score, the CLIF-C ACLF score.. The CLIF-C ACLF score combines CLIF-OF score with patients' age and white blood cell (WBC) count to generate a composite score of 0–100 in a linear range. Validation in an external prospective cohort showed that this score was significantly more accurate than Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, and MELD with serum sodium score in predicting 28-day mortality in ACLF. CLIF-C ACLF score predicted short-term mortality 25% better than all listed scores. The 28-day mortality varied from below 20% in CLIF-C ACLF

score < 45 to more than 80% in CLIF-C ACLF score ≥ 65. **(15)** .

The utility of CLIF-C ACLF score in patients with ACLF grade 3, and specifically CLIF-C ACLF score > 64, has been discussed **(13))** because these patients may still have a poor prognosis in spite of maximal treatment efforts and the associated high costs. Validating the CLIF-C ACLF score on the dataset of the CANONIC (EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis) study has shown that in a subset of patients with four or more organ failures and/or CLIF-C ACLF score ≥ 65, 3–7 days after ACLF diagnosis, mortality rates were 100%. Single-center experiences in a small subset of such patients with ACLF ($n = 23$). **(13)** supported this notion, albeit that mortality in this cohort was lower at 86% after 90 days. **(30)** . As a consequence, it has been suggested that intensive care support could be withdrawn in patients with this severity of disease. However, because the available data to support this notion are restricted to the CANONIC cohort and one small, single-center, study, further validation is required before this can be considered for translation into clinical practice.

References

1. Dooley S, ten Dijke P. Et al.(2012), TGF-β in progression of liver Disease. Cell Tissue Res;347(1):245-256.
2. Asrani SK, Kouznetsova M, Ogola G et al., (2018), Increasing Health Care Burden of Chronic Liver Disease Compared With Other Chronic Diseases, 2004-2013. Gastroenterology. S;155(3): 719-729.
3. Hu, Y., Chen, D., Li, Q., Yin, G., Zhang, X., & Wang, Y. (2022). A prediction model for 30-day deaths of cirrhotic patients in intensive care unit hospitalization. Medicine, 101(5), e28752.
4. Lee, H. A., Jung, J. Y., Lee, Y. S., Jung, Y. K., Kim, J. H., An, H., Yim, H. J., Jeen, Y. T., Yeon, J. E., Byun, K. S., Um, S. H., & Seo, Y. S. (2021). Direct Bilirubin Is More Valuable than Total Bilirubin for Predicting Prognosis in Patients with Liver Cirrhosis. Gut and liver, 15(4), 599–605.
5. Fernández, J., Aracil, C., Solà, E., Soriano, G., Cinta Cardona, M., Coll, S., Genescà, J., Hombrados, M., Morillas, R., Martín-Llahí, M., Pardo, A., Sánchez, J., Vargas, V., Xiol, X., & Ginès, P. (2016). Evaluación y tratamiento del paciente cirrótico crítico [Evaluation and treatment of the critically ill cirrhotic patient]. Gastroenterologia y hepatologia, 39(9), 607–626.
6. Cheemerla, S., & Balakrishnan, M. (2021). Global Epidemiology of Chronic Liver Disease. Clinical liver disease, 17(5), 365–370.
7. Moreau, R., Jalan, R., Gines, P., Pavesi, M., Angeli, P., Cordoba, J., Durand, F., Gustot, T., Saliba, F., Domenicali, M., Gerbes, A., Wendon, J., Alessandria, C., Laleman, W., Zeuzem, S., Trebicka, J., Bernardi, M., Arroyo, V., & CANONIC Study Investigators of the EASL–CLIF Consortium (2013). Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology, 144(7), 1426–1437.e14379.
8. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973). "Transection of the oesophagus for bleeding oesophageal varices". The British Journal of Surgery. 60 (8): 646–9.
9. Ho, Y. P., Chen, Y. C., Yang, C., Lien, J. M., Chu, Y. Y., Fang, J. T., Chiu, C. T., Chen, P. C., & Tsai, M. H. (2004). Outcome prediction for critically ill cirrhotic patients: a comparison of APACHE II and Child-Pugh scoring systems. Journal of intensive care medicine, 19(2), 105–110.
10. Jain R, Kralovic SM, Evans ME, Ambrose M, Simbartl LA, ObroskyDS, et al. Veterans Affairs initiative to prevent methicillin-resistant Staphylococcus aureus infections. N Engl J Med 2011;364:1419-1430.
11. Olson, J. C., Wendon, J. A., Kramer, D. J., Arroyo, V., Jalan, R., Garcia-Tsao, G., & Kamath, P. S. (2011). Intensive care of the patient with cirrhosis. Hepatology (Baltimore, Md.), 54(5), 1864–1872.
12. Bernard, B., Grangé, J. D., Khac, E. N., Amiot, X., Opolon, P., & Poynard, T. (1999). Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology (Baltimore, Md.), 29(6), 1655–1661.
13. Fernandez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G,et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818-824.
14. Valla D. C. (2008). Thrombosis and anticoagulation in liver disease. Hepatology (Baltimore, Md.), 47(4), 1384–1393.
15. Jalan, R., Pavesi, M., Saliba, F., Amorós, A., Fernandez, J., Holland-Fischer, P., Sawhney, R., Mookerjee, R., Caraceni, P., Moreau, R., Ginès, P., Durand, F., Angeli, P., Alessandria, C., Laleman, W., Trebicka, J., Samuel, D., Zeuzem, S., Gustot, T., Gerbes, A. L., … CANONIC Study Investigators; EASL-CLIF

Consortium (2015). The CLIF Consortium Acute Decompensation score (CLIF-C Ads) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. Journal of hepatology, 62(4), 831–840.
16. Luca, A., Angermayr, B., Bertolini, G., Koenig, F., Vizzini, G., Ploner, M., Peck-Radosavljevic, M., Gridelli, B., & Bosch, J. (2007). An integrated MELD model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society, 13(8), 1174–1180.
17. Theocharidou, E., Pieri, G., Mohammad, A. O., Cheung, M., Cholongitas, E., Agarwal, B., & Burroughs, A. K. (2014). The Royal Free Hospital score: a calibrated prognostic model for patients with cirrhosis admitted to intensive care unit. Comparison with current models and CLIF-SOFA score. The American journal of gastroenterology, 109(4), 554–562.
18. Child CG, Turcotte JG (1964). "Surgery and portal hypertension". In Child CG (ed.). The liver and portal hypertension. Philadelphia: Saunders. Pp. 50–64.
19. Campbell, J., McPeake, J., Shaw, M., Puxty, A., Emerson, P., Thomson, S. J., Rahman, T. M., Quasim, T., & Kinsella, J. (2015). Validation of a prognostic scoring system for critically ill patients with cirrhosis admitted to ICU. Journal of the Intensive Care Society, 16(3), 240.
20. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonaldLC, et al.; for Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31: 431-455.
21. Working Subgroup (English version) for Clinical Practice Guidelines for Primary Biliary Cirrhosis (2014-01-01). "Guidelines for the management of primary biliary cirrhosis". Hepatology Research. 44: 71–90.
22. Everhart, J. E., & Ruhl, C. E. (2009). Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology, 136(4), 1134–1144.
23. Søgaard, K. K., Horváth-Puhó, E., Grønbaek, H., Jepsen, P., Vilstrup, H., & Sørensen, H. T. (2009). Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. The American journal of gastroenterology, 104(1), 96–101
24. About third of study populations (33.8%) died within medical ICU.
25. Zocco, M. A., Di Stasio, E., De Cristofaro, R., Novi, M., Ainora, M. E., Ponziani, F., Riccardi, L., Lancellotti, S., Santoliquido, A., Flore, R., Pompili, M., Rapaccini, G. L., Tondi, P., Gasbarrini, G. B., Landolfi, R., & Gasbarrini, A. (2009). Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. Journal of hepatology, 51(4), 682–689.
26. Liu, Z., Jiang, Y., Yuan, H., Fang, Q., Cai, N., Suo, C., Jin, L., Zhang, T., & Chen, X. (2019). The trends in incidence of primary liver cancer caused by specific etiologies: Results from the Global Burden of Disease Study 2016 and implications for liver cancer prevention. Journal of hepatology, 70(4), 674–683.
27. Dooley S, ten Dijke P. Et al.(2012), TGF-β in progression of liver Disease. Cell Tissue Res;347(1):245-256.
28. Abdellatif, Z., Eletreby, R., Samir, R., Abdallah, M., Lithy, R., & Zayed, N. (2022). Outcome and prognostic markers of cirrhotic and non-cirrhotic patients admitted to a hepatology ICU in a tertiary care university hospital. African health sciences, 22(2), 377–383.
29. Olson, J. C., Wendon, J. A., Kramer, D. J., Arroyo, V., Jalan, R., Garcia-Tsao, G., & Kamath, P. S. (2011). Intensive care of the patient with cirrhosis. Hepatology (Baltimore, Md.), 54(5), 1864–1872.
30. Kaeppeli, T., Rueegg, M., Dreher-Hummel, T., Brabrand, M., Kabell-Nissen, S., Carpenter, C. R., Bingisser, R., & Nickel, C. H. (2020). Validation of the Clinical Frailty Scale for Prediction of Thirty-Day Mortality in the Emergency Department. Annals of emergency medicine, 76(3), 291–300.