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MORTALITY AND ITS ASSOCIATED FACTORS OF ACUTE LIVER FAILURE IN HOSPITALIZED MEDICAL PATIENTS IN TIBEBE GHION SPECIALIZED HOSPITAL AND FELEGE HIWOT HOSPITAL, BAHIR DAR, ETHIOPIA

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MARCH 2024GC

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A RESAERCH THESIS TO BE SUBMITTED TO BAHIR DAR UNIVERSITY,COLLEGE OF MEDICINE AND HEALTH SCIENCE , SCHOOL OF MEDICINE,DEPARTMENT OF INTERNAL MEDICINE COLLEGE OF MEDICINE AND HEALTH SCIENCES IN PARTIAL FULLFILMENT OF THE REQUIREMENTS FOR THE SPECIALITY PROGRAM OF INTERNAL MEDICINE

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MARCH 2024GC

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Declaration

This is to certify that the thesis entitled“mortality and its associated factors of acute liver failure” , submitted in partial fulfillment of the requirements for the degree of internal medicine specialization,Department of internal medicine, Bahir Dar University, is a record of original work carried out by me and has never been submitted to this or any other institution to get any other degree or certificates. The assistance and help I received during the course of this investigation have been duly acknowledged.

Name of the candidate	Signature	Date

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Abstract

Background: acute liver failure is hepatic encephalopathy with coagulopathy without preexisting liver disease.it can cause multi organ failure and high risk of mortality (60-80%). Globally the prevalence of acute liver failure is 5 cases in 100000 and2000 cases/year in US.Its prevalence is much higher in developing countries explained by study done in India in which the prevalence of hepatic failure is 8%. Therefore, assessing the burden of acute liver failure mortality and its possible risk factors in the institution is significant for evidence-based interventions and it is a good opportunity to update the magnitude of acute liver failure mortality in the institutions.

Objective: to determine the in hospital mortality and associated factors of acute liver failure in hospitalized medical patients from September1, 2017 to August 30, 2023 in TibebeGhion specialized hospital and Felegehiwot compressive and specialized hospital, Bahirdar.

Methods: Institution-based cross-sectional study was conducted among the 152 adult population. A convenience sampling method was use. Data was collected by retrospective chart review for patients admitted to medical wards and ICU by using the pre-developed data collection format. Data wasentered to SPSS version27 software database for analysis. multivariate logistic regression model was used to identify factors associated with acute liver failure mortality and was presented by adjusted odds ratio (AOR) with 95% of CI. The model fitness was checked using Hosmer-Lemeshow at significance test at P values < 0.05.Multivariate analysis was carried to assess the relations of dependent and independent variables at p-value less than 0.05. 95% confidence and p-value will be used to measure the association.

Results: Overall, the proportion of acute liver failure mortality among adult medical patients admitted in Tibebegion and FelegeHiwot was 78.3% (95%CI, 71.7 – 84.9%). In multivariable logistic regression analysis, age (AOR = 1.119, 95%CI, 1.034 – 1.211,p=0.005), admission mental status (grade 3 ,AOR = 8.2, 95%CI, 1.101 – 61.5,p=0.04& grade 4, AOR = 11.14, 95%CI, 1.23 –100.8,p=0.032), GI bleeding (AOR = 17.6, 95%CI, 2.23 – 139.5,p=0.006) and AKI (AOR = 7.18, 95%CI, 1.19 – 43.2,p=0.03),herbal medication exposure(AOR=7.28,95%CI,1.33-39.8,P=0.022), coagulopathy(INR,AOR =1.99, 95%CI, 1.12 – 3.54,p=0.019 and PT,AOR =1.2, 95%CI,1.05-1.40,p=0.009),total bilirubin(AOR = 1.12, 95%CI, 1.006 – 1.26,p=0.039), serum sodium(AOR = 0.81, 95%CI, 0.68 – 0.96,p=0.018),RBS level

(AOR = 0.98, 95%CI, 0.96 – 0.99,p=0.024), were statistically significant associated factors with acute liver failure mortality.Gender, residency, serum potassium level, BUN leve,APTT prolongation ,serum level of liver enzymes, the rapidity of onset of encephalopathy, lower grade(≤2 grade), hepatic encephalopathy, pregnancy and being postpartum did not influence the outcome.

Conclusions: The overall proportion of ALF mortality is high in this study. age, higher grade hepatic encephalopathy(grade 3& grade 4),GI bleeding, AKI, coagulopathy, total bilirubin level, serum sodium ,blood sugar level and herbal medication exposure were found to be a significant associated factors that predict acute liver failure mortalityindepedently. Therefore it is crucial to combat these factors to improve ALF mortality.

Work plan and budget: The work plan of this project was finalized in one year and seven months from June 2022 to January 2024 GC and fund (28118.2Birr) was obtained from Bahir Dar University research office.

Key words: acute liver failure, medical ward, in patient

Lists of Acronyms and Abbreviations

ALF……ACUTE LIVER FAILURE

ALP……ALKALINE PHOSPHATASE

ALT…….ALANINE AMINOTRANSFERASE

Anti-TB-DIH….ANTITUBERCULOSIS DRUG IINDUCED LIVER INJURY

ART……..ANTIRETROVIRAL THERAPY

AST……...ASPARTATE AMINOTRANSFERASE

LDLT……...LIVING DONOR LIVER TRANSPLANT

INR……...INTERNATIONAL NORMALIZED RATIO

APTT……ACTIVATED PARTIAL THROMBOPLASTIN TIME

PT……PROTHROMBIN TIME

BUN……BLOOD UREA NITROGEN

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Chapter one: Introduction

1.1. Back ground

Acute liver failure (ALF) is defined as any degree of hepatic encephalopathy with coagulopathy (INR>1.5) that occurs within 26 weeks and should not have pre-existing liver disease (1).it is classified into three to accurately reflect important differences in clinical features and prognosis. These includes: Hyperacute-for cases in which encephalopathy occurs within 7 days of the onset of jaundice; this group includes the sizeable cohort likely to survive with medical management despite the high incidence of cerebral oedema. acute - for cases with an interval of between 8 and 28 days from jaundice to encephalopathy; they also have a high incidence of cerebral oedema, but have a much poorer prognosis without liver transplantation. The term subacute- is suggested to describe cases with encephalopathy that occurs within after 28 days after onset of jaundice; these patients are characterised by a low incidence of cerebral oedema, but have a poor prognosis(2).

ALF is an infrequent condition, with an incidence of 1–8 cases per million inhabitants, and it is responsible for 6% of deaths due to liver disease and up to 7–8% of liver transplants(3). Acute liver failure is much less common in the developed world than in the developing world(4). The mortality due to ALF in the pre transplant era was extremely high, often exceeding 90%. The causes of death typically include multi organ failure, hemorrhage, infection, and cerebral edema**(5)**. In spite of the improvement of medical system and advancement in liver transplantation, the overall mortality of ALF remains 20%-40%, the major reasons of which are the rapid disease progression and the highly unpredictable outcomes depending on various factors**(6).**ALF mainly affects young adults, with a peak age between 35 and 45 years and Women account for approximately 60% of cases(7).

In the developing world, viral causes predominate, with hepatitis E infection being a common cause in many countries. In the USA and much of western Europe, the incidence of virally induced disease has declined in the past few years, with most cases now arising from drug-induced liver injury, often from paracetamol(8).

1.2. Statement of the problem

Acute liver failure is a rare clinical syndrome with an annual incidence of less than 10 cases per million population in the developed world but it is more common in developing countries due to the higher incidence of infectious hepatitis in these regions(9). Acute liver failure (ALF) is a clinical syndrome with reported mortality estimates ranging between 60 and 80% depending on the cause, the care and associated factors(10).

Acute liver failure accounts for 6%–9% of all liver transplant activity in the US and Europe(11)

Etiologies vary between Western countries and the developing world. In Europe and North America most cases are due to acetaminophen and to idiosyncratic drug reactions, whereas in Asia and Africa viral illnesses are the predominant cause, particularly hepatitis B and E. Determining etiology is important for two reasons: specific antidotes or therapies may be indicated once the diagnosis is known, and knowing the cause provides a reasonably valid guide to predicting outcome(12).acute liver failure causes multiorgan failure including acute kidney injury ,infection ,mental status change, bleeding and acute respiratory distress syndrome and cardiovascular disturbance(13).

Acute liver failure can present with multi organ failure initially with non-specific symptoms like fatigue, anorexia, nausea, abdominal pain ,fever, jaundice and later hepatic encephalopathy and coagulopathy(14).

Treatment is directed at early recognition of etiologies, complications and general supportive measures. The only proven therapy for those who are unlikely to recover is liver transplantation. Therefore, recognition of ALF and its etiology is paramount, and urgent referral to a transplant center is critical to assess transplantation(15).

Studies on ALF are relatively fewer in the world and in Africa and even no study in Ethiopia because of its rarity and in depth discrepancies in the definitions(16).

Therefore, assessing the burden of ALF mortalityand possible risk factors in the institutions is significant for evidence-based interventions and it is a good opportunity to update the proportion of ALF mortality.

1.3. Significance of the study and justification

Studying the mortality and its associated factors of acute liver failure helps to intervene early after the occurrence of the disease and to prevent the occurrence of the disease by understanding the epidemiology of modifiable risk factors and to prevent herbal medication induced acute liver failure by increasing public awareness of risk of non-studied herbal medication through health education. Studying the mortality also helps to understand the outcome burden and for health care advancement plan for health institution for the future.

Chapter two: Literature review

2.1. Associated factors

In a cohort study done in England, arterial blood lactate level measured at earlier(median 4hr) and post resuscitation(median of 12hr) after admission , median lactate was significantly higher in non-surviving patients than in survivors both in the early samples (8·5 [range 1·7–21·0] vs 1·4 [0·53–7·9] mmol/L, p<0·0001) and after fluid resuscitation (5·5 [1·3–18·6] vs 1·3 [0·26–3·2], p<0·0001) and both have similar predictive ability to identify non surviving patients with ALF earlier (4 [3–13] vs 10 [3·5–19·5] h, p=0·01)(17).Another study in Germany shows that high levels in the following parameters significantly associated with increased mortality in ALF, lactate level(>3.5mmol/l),bilirubin>140umol/l or 1.6mg/dl),BILE score>6.9,MELD score >32(all with p<=0.001)(18).In another study in saudiArbia,age >40 years, male gender, PEP >7 days, coma grade >2, occurrence of cerebral oedema, sepsis and renal failure at presentation, prothrombin time >30 s, and non-E aetiology were differed significantly between survivors and non-survivors on univariate analysis.Of these variables, those associated with ALF mortality significantly on mutiviariant analysis were ALF caused by non-hepatitis E agents (OR =20(95%CI 2.3–21.4),p=0.003), prothrombin time >30s (OR =9.3 (95%CI 1.3–50.6),p=0.04),grade of coma >2(,OR=7.5 95%CI(3.3–61.9),p=0.006) andAge >40 years (OR=4.7 ,95%CI 1.8–344),p=0.003) but Pregnancy per se or duration of gestation did not adversely affect the prognosis(19).study in India on antituberculosis induced acute liver failure ,multivariate analysis with logistic regression showed that serum bilirubin (>10.8 mg/dL)(p=0.001), PT prolongation (>26 seconds) (p=0.005), and grade III/IV hepatic encephalopathy(p=0.043), at presentation were independent predictors for mortality; odds ratios

were 13.08, 6.81, and 6.08, respectively. however none of the Age (p= 0.132), Sex (p= 0.956) Pregnancy (p=1.00), Icterus—encephalopathy interval (p= 0.647), ATT–ALF interval (p= 0.121), Sites of tuberculosis(p= 0.440), AST (IU/L) (p= 0.189),ALT (IU/L)(p=0.394), Alkaline phosphatase (U/L) (p= 0.994), Albumin (mg/dL)(p=0.969), Blood urea (mg/dL)(P= 0.707),Serum creatinine (mg/dL) (p= 0.807) are associated with mortality(20).According to study done in india, an increase or persistent elevation of predictor variable over 3 days, increases ALF mortality.Predictors of mortality, Variables at admission are advanced HE (grade >2) (OR= 2.31 (1.5 to 3.4),p<0.001), INR >5(OR= 3.17 (2.11 to 4.77),p= <0.001), Arterial ammonia >123 mmol/l(OR= 2.33 (1.22 to 4.47) p=0.01)), Serum bilirubin >15 mg/dl(OR=1.00 (1.00 to 1.07),p= 0.02)) and Predictors of mortality based on variables dynamicity over 3 days are HE, persistent or progressed to grade >2(OR=13.5 (5.9 to 30.7) ,p <0.001), INR, persistent or increased to levels >5 (OR=3.42 (1.5 to 7.5),P= 0.002), Arterial ammonia, persistent or increased to level >123 mmol/l(OR=10.8 (4.7 to 24.4) <0.001), Serum bilirubin, persistent or increased to level >15 mg/dl(OR=1.04 (1.0 to 1.09) ,P=0.05)(21).another study in US,show that In multivariate analysis , age (odds ratio [OR] 1.37 per decade), coma grade (OR 2.02 grade 2, 2.65 grade 3, 5.29 grade 4), MELD (OR 1.07), and pH < 7.4 (OR 3.09), were significantly associated with ALF mortality(22). In study done in Uruguay, the variables associated with increased mortality in acute liver failure are higher MELD scores at admission (mean 37 vs 28) and highest achieved (mean 42 vs 29; P < .001 in both cases) and a higher proportion of HE grades III to IV than the survivors (94% vs 25%, P < .001). The proportion of unfavorable etiologies, subacute impairment and age was higher among dead patients, but no significance could be demonstrated. Patients who died had a longer referral time than those who survived (median 10 vs 4 days, P =0 .008)(23). Etiology did significantly impact survival, with Favorable etiologies having an average spontaneous survival rate of 68%, compared to 27% for Unfavorable etiologies(24).

2.2. Causes of the disease

the prevalence of Causes of acute liver failure vary geographically.drug induced liver injury(DILI) is currently one of the most common causes of acute liver failure in the world with crude incidence of 2.4 cases per 100000 annually(25). Viral hepatitis and drug-induced liver injury (DILI) are the most common etiologies worldwide. Asian and African countries have a higher incidence of hepatotropic viral infection, particularly hepatitis A, B and E. In contrast, Europe and the US have a higher incidence of DILI, particularly by acetaminophen(26).In low-

income and middle-income countries (LMICs), indeterminate causes, traditional medicines, drugs (including anti-tuberculosis medications), herbal supplements, and alcohol are some of the other causes of acute liver failure(27).

The incidence of drug induced liver injury in Europa varies country to country as studies done inSweden(2.3/100000)(28),france(14/100000)(29),Iceland(19/100000)(30),unitedkingdom(8.8%)(31),Switzerland(1.4%)(32).In these countries antibiotics were the most common cause of DILI. The most commonly implicated drugs were amoxicillin-clavulanic acid (22%), diclofenac (6%), azathioprine (4%), infliximab (4%), and nitrofurantoin (4%)(30) but study done in Germany shows that drugs for neurologic disorders are the most common cause of DILI(33).

Other studies in different European countries show different causes of acute liver failure as studies done

In United kingdom acetaminophen DILI is the most common cause which cause 57% of ALF followed by non-acetaminophen DILI in 11%,hepatitis B in 5%,hepatitis E in 1%,hepatitis A in 2%,miscellaneous cause in 7% and unknown causes in 17% cases(34).whereas in Germany in 21% of cases of ALF cause is unknown and in 14% of cases of ALF cause is non-acetaminophen DILI followed by acetaminophen DILI in 15% of cases, hepatitis B in 18% of cases, hepatitis E in 4% of cases, hepatitis A in 4% of cases and miscellaneous causes in 24% of cases(35).In contrast to the above in Spain hepatitis B is the most common causes accounting 32% of ALF followed by non-acetaminophen DILI(14%), acetaminophen DILI(2%),hepatitis A(2%),miscellaneous causes(32%),unknown cause(18%)(36).

DILI is the most frequent cause of acute liver failure in the USA (37-39). A study done in united states shows 50% of acute liver failure is caused by drugs(acetaminophen is most common(42-46%) and around 11% is caused by non-acetaminophen drugs),hepatitis B(8%),hepatitis A(2%), miscellaneous causes(14%),unknown cause(19%)(40).

Another study done in California shows the incidence of acute liver failure is 9.3% of which 51.6% is caused by drug induced etiology(acetaminophen in 56.3%,dietary/herbal supplement in 18.8%,antimicrobials in 6.3% and miscellaneous medications in 18(41).

Study done in Australia shows that 42% of ALF is caused by acetaminophen DILI,6% by non-acetaminophen DILI,8% by hepatitis B,5% by hepatitis A, 28% by miscellaneous causes and in 11% of cases the cause is unknown(42).

According to studies done in different Asian countries the causes of acute liver failure also vary country to country.Injapan hepatitis B is the most common cause of acute liver failure which occurs in 42% of the cases followed by miscellaneous causes(34%), non-acetaminophen DILI(9%),unknown cause(7%) hepatitis A(7%)(43).similar to japan in Pakistan hepatitis B is the most common cause which occurs in 37% of cases followed by hepatitis E(25%),miscellaneous causes(23%),unknown causes(12%) and non-acetaminophen DILI(3%)(44).In contrast in China the most common cause ALF is non-acetaminophen DILI in 32% followed by miscellaneous causes(29%),unknown causes(17%) ,acetaminophen DILI(12%), hepatitis E(7%) and hepatitis B(3%)(6, 45) where as in India in 31% of the cases causes of ALF is unknown followed by hepatitis E(44%), hepatitis B(15%), hepatitis A(2%) and non-acetaminophen DILI(1%)(46, 47).

studies done in different Asian countries like in Singapore (48), Korea in 70% of cases(49, 50),china in 36% of cases(51),japan(52),Thailand(53) ,Taiwan(54) and India in 72% of the cases(55, 56), the most common cause of non-acetaminophen DILI is traditional and herbal medication. Another study in china mainland shows that DILI is caused by traditional and herbal medication in 27% of the cases followed by anti-tb drug in 22% of the cases(57) but in Nepal and Malaysia burden of DILI is 8-9.4%(58, 59).

In Africa causes of acute liver failure also vary country to country. In Egypt, the burden of drug induced liver injury is 11.5-15%(60) but in Sudan 38% of ALF is caused unknown causes,27% other causes,22% hepatitis B,8% non-acetaminophen DILI and 5% hepatitis E(61).

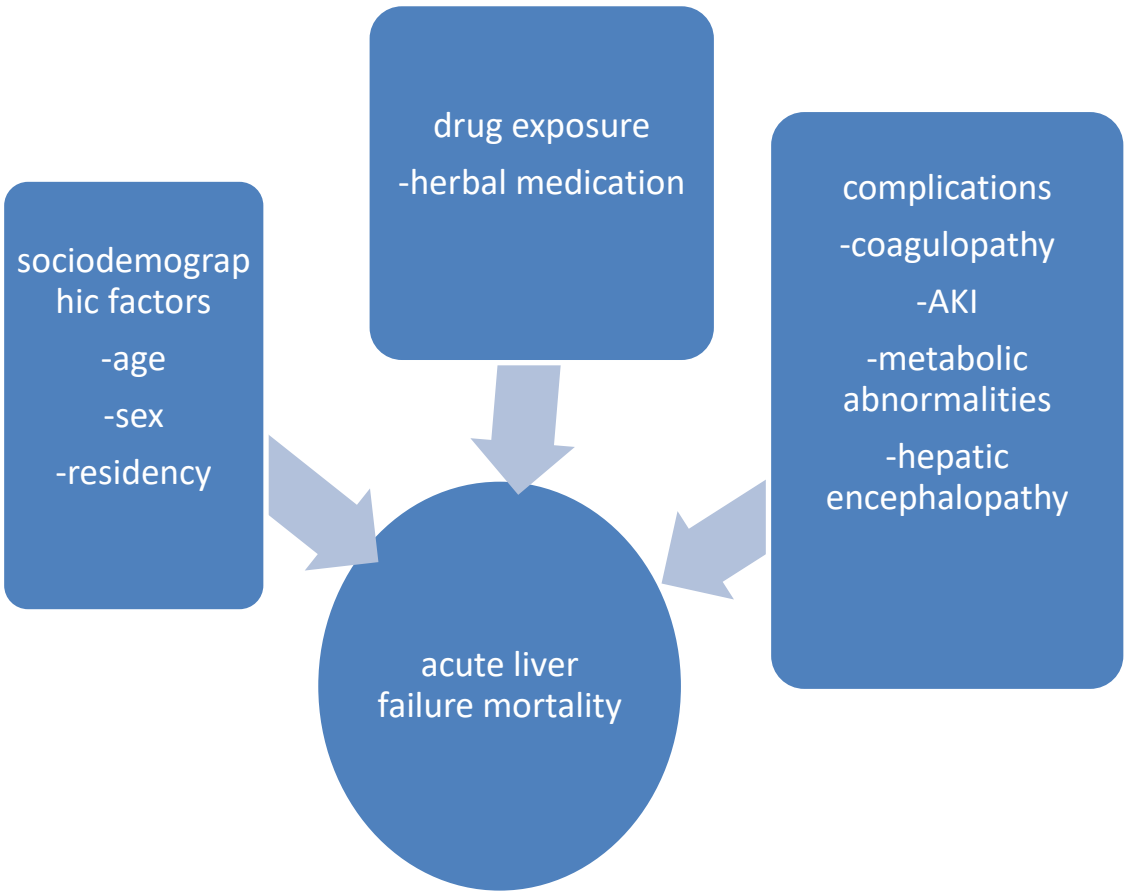
According to studies done in Ethiopia the incidence of drug induced liver injury varies geographically. In Dawro anti tb drug induced acute liver injury is 8%(62).

According to study done in debrebirhan hospital the incidence of HAART drug induced liver injury is 25% and the only associated factor that increases HAART induced DILI is BMI .Patient's whose body mass index (BMI) existed between 18.6 and 24.9 were 3 times more likely to developing DILI but socio-demographic and clinical variables didn't show any statistical significant ($p > 0.05$)(63).

According to studies done in Ethiopia the prevalence of viral hepatitis varies region to region.Dawro zone(13.5%)(62) and Jimma(11.5%)(64) have similar prevalence of viral hepatitis but it is lower in Debremarkos(7.9%)(65) and in Addis Ababa acute viral hepatitis incidence varies based on etiology: hepatitis A(8%),hepatitis B(20%),hepatitis E(33%),hepatitis C(19%) and NANB hepatitis cause(39%)(66).

But the abovestudies neither determinewhich etiologies are the most common cause of acute liver failure nor the burden of acute liver failure in Ethiopia.

2.3. Conceptual frame work



3. Objectives of the study

3.1. General objective

- ✓ To assess mortality and its associated factors of acute liver failure in admitted medical patients from September 1, 2018 to august 30, 2023 in TibebeGhion specialized hospital and Felegehiwot hospital, Bahirdar.

3.2. Specific objective

- ✓ To determine acute liver failure mortality
- ✓ To identify associated factors of acute liver failure mortality

4.Methods and materials

4.1. Study design

Institution based Cross sectional study was applied

4.2. Study Area and Period

Bahir Dar is situated on the southern shore of Lake Tana, the source of the Blue Nile (locally called Abay). Bahir Dar city (one of the ten most beautiful cities in Africa and one of the twelve UNESCO Learning Cities Awardee of 2015) .The city is located approximately 578 km (360 miles) north-northwest of Addis Ababa, and an elevation of 1,840 meters (6,036 foot) above sea level. TibebeGhion specialized hospital is located about 10km south from the city center and about 7 km from the new bus station ('AddisuManhuria') on the way to Adet District and about 23 km from the Blue Nile Falls (locally called 'TisEsat' (Smoke of Fire). It is a tertiary university teaching hospital with 450 bed capacity out of which 72 are occupied by medical adult patients. The hospital receives patients who are referred from across the Amara region and gives outpatient and inpatient services in all major departments. Felegehiwot hospital is referral hospital located in bahirdar on the southern border of the city and there is lot of patient burden in the hospital. The study was conducted in Tibebeghion specialized hospital and Felegehiwot hospital starting from September 1, 2018 to august 31, 2023G,C.

4.3. study period

The study period was from September 1, 2018 to August 31, 2023

4.4. Source Population

All adult patients with ALF admitted to Tibebeghion and FelegeHiwot hospital.

4.5. Study population

Medical patients who were admitted with diagnosis of acute liver failure to medical ward and ICU in Tibebeghion hospital and Felegehiwot hospital from September 1, 2018 to august 31, 2023were the study population.

4.6. Inclusion criteria

Age ≥18 years

Patients admitted with established acute liver failure

4.7. Exclusion criteria

Patients with established chronic liver disease

Patient with incomplete medical record

4.8. Study variables

4.8.1. Dependent variable

Acute liver failure mortality (yes/no)

4.8.2. Independent variables

Demographic factors (age, sex), associated factors of acute liver failure mortality (causes, complications)

4.9..Operational definition

- Acute liver failure-liver injury explained by coagulopathy(INR>1.5) and hepatic encephalopathy that occurs with in 26 weeks in the absence of established chronic liver disease(67).
- Acute kidney injury-refers to an abrupt decrease in kidney function resulting in retention of urea and other nitrogenous waste products and diagnosis was made based on KDIGO diagnostic criteria either one or more of the following criteria fulfilled i) increase in

serum ceatinine level from the baseline by >=0.3 mg/dl within 48 hours or ii) increase in serum creatinine to >=1.5x baseline, whch is known or presumed to have occurred within the prior 7 days or iii) when urine volume <0.5ml/kg/hr for six hours(68).

- GI bleeding- diagnosis was when there is bloody vomiting or when there is blood per rectum during the time of hospitalization with ALF.
- herbal medication exposure-any supplementary preparation given to the patients per oral in the last 3 months in the last 3 months(69).
- Hepatic encephalopathy-Hepatic encephalopathy (HE) is a significant complication of severe acute or chronic liver insufficiency that is characterized predominantly by alterations of personality, consciousness, cognition and motor function. Three types of HE are traditionally differentiated according to the underlying cause: Type A as an essential component of acute liver failure, type B as a consequence of porto-systemic shunts in the absence of liver dysfunction and type C in patients with liver cirrhosis and porto-systemic bypass .The West Haven criteria (WHC) are the most frequently used for grading HE . This grading system differentiates four grades of clinically manifest HE . In grade I, patients show a lack of attention and some subtle personality changes that are obvious predominantly to their relatives. In grade II, the most intriguing finding is disorientation for time combined, for example, with inappropriate behavior and lethargy. In grade III, patients are stuporous but respond to stimuli. They are also disoriented for place and situation and may exhibit bizarre behavior. In grade IV, patients are in coma(70).

4.10.Sample size and sampling procedure

The sample size will be determined by using the following assumptions ;the proportion in previous study is 90%**(**5)**,**95% confidence level(1.96),precision level of 0.05.by using single population formula and based on the above assumptions, the estimated sample size is 138.by adding the 10% non-response rate total sample size is 152.

$$n \geq \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

Where n= sample size

Za½=standard normal distribution corresponding 95% significance= 1.96

P = estimated proportion of acute liver failure mortality in previous studies=90%

d = desired precision =5%

n = (1.96)2 (0.093) (0.907)/ $(0.05)^2$

n = 138.29=138

Due to the rarity of the case, all patients with ALF during the study period were taken as sample. All eligible patients admitted with acute liver failure to TibebeGhion specialized hospital and Felegehiwot comprehensive and referral hospital from September 1, 2017 to august 31, 2023 were considered as a sample. During this period in both hospitals, a total of 157 ALF patients were admitted in medical ICU and medical ward. Among these 5 patients were excluded (3 had no complete medical record, 1 had cirrhosis and 1 with age <18 years). so, the sample size became 152, which is similar with the above calculated sample size with 10% non response rate. The sampling technique was convenience sampling .

4.11. Data collection procedure

Pre-developed data collection format was used to collect data on patient's socio-demographic characteristics ,coagulation profile(APTT,PT and INR),mental status of the patient and metabolic abnormalities(serum electrolyte, blood sugar level, liver enzymes, liver synthetic functions and liver execratory function) by retrieving first the admission medical record number from registration book and then patient's card from card room.

4.12. Data quality assurance

The data was collected by trained health professionals (2-nurses who work in medical wards and icu&1-medical resident). Training was given how to collect the data. Data collection was supervised by principal investigator.

4.13. Data processing and staticalanalysis

The principal investigator checked the collected data and any incomplete documents was cleaned, checked for quality prior to data entry. Data was enteredto Statistical Package for Social Sciences (SPSS) software version 27 and analyzed. All variables were cleaned by running simple frequencies to avoid missing values and checked formulticollinarityand for fulfillment of assumptions. continuous variables were analyzed for normality distribution using distribution curve(graphical method). The descriptive statics (mean and standard deviation for continuous variables; and frequencies and percentages for categorical variables) was computed, and the results were presented by tables and bar graphs,Univariate analysis was performed to compare survivors and non survivors using an independent t test for normally distributed continuous variables, andchi-squared test for any other categorical variables. A P-value of less than 0.05 was taken as significant.Bivariate logistic regression was used to explore the association between acute liver failure mortality and each independent variable. P-value ≤ 0.25 cutoff points wasconsidered to select potential candidates for the full model multivariant analysis.Finally, a multivariate logistic regression model was used to identify factors associated with acute liver failure mortality and was presented by adjusted odds ratio (AOR) with 95% of CI .The model fitness was checked using Hosmer-Lemeshow at significance test at P values < 0.05.Multivariate analysis was carried to assess the association of dependent and independent variables at p-value less than 0.05. 95% confidence and p-value was used to measure the association.The levels of liver tests immediately on admission were used for analysis.All variables included in determining the prognosis were those recorded at presentation. For renal failure and gastrointestinal bleeding findings recorded throughout the course of hospitalization were included for analysis .primary outcome was defined as spontaneous survival or death. No patient underwent transplantation.

5.. Ethical considerations

Ethical clearance and approval letter was obtained from Bahir Dar University,medical college, Ethics Review Committee. Then a formal letter of permission to conduct the study was taken, from TibebeGion hospital administrative office and FelegeHiwot medical administrative and quality assurance officer. Name was not used in collecting the data from the medical files. Confidentiality was maintained by keeping the data collection forms locked in a secure cabinet

and the electronic data file was kept securely in a password protected computer. Data obtained in the course of study was only be handled by the research team.

CHAPTER THREE

3.1. Results

3.1.1. Sociodemographic characteristics,clinical data and laboratory data

The mean ± (SD) age of the study was 39.17±13.5 years. The majority (53.9%) of the patients were below age 39 years. Of the 152 patients with acute liver failure, 103(67.8%) live in countryside and 81(53.3%) were women, of whom 21(13.8%) were pregnant and 17(11.2%) were in the postpartum period. Exact data on the duration of jaundice before onset of encephalopathy were available for all of the patients. The mean interval between jaundice and onset of encephalopathy was 7.6±4.6days overall and it is longer in non-survivors (7.9±4.9 days)than survivors(6.7±2.9days).In this study, 40.8% (95%CI, 33.6 – 48.7%) patients have AKI and most AKI (90.3%) occur in non survivors. this study also shows 23% (95%CI,13.2 – 26.3%) patients have GI bleeding and most of the GI bleeding (85.7%) occur in the non survivors.All of the patients have at least grade 1 hepatic encephalopathy. Majority, 107 (70.4%) had high-grade (grade 3/4) encephalopathy at admission. Majority,13(48.1%) of surviving patients have grade 1 hepatic encephalopathy and majority, 49(89.1%) of the non-surviving patients have grade 3 hepatic encephalopathy. out of total populations(152),26.3% had taken herbal medication per mouth within 3months prior to the current presentation.

Coagulation profile of the patients in the study shows that the mean value of INR,PT and APTT are 5.57,59.2 and 40.8 respectively and majority, 57.2%,59.9% and 59.2% of the patients have INR,APTT and PT level below the mean value ,respectively.

the mean value of RBS , sodium ,potassium and total bilirubin are 111.09,138.17,3.68 and 10.81 respectively.overall,Details are presented in Table 1.

Table 1 sociodemographic characteristics and clinical data of patients in tibebegion and Felegehiwot hospitalexpressed as frequency and percentage for categorical variables and means+-SD for continous variables

Variables	Categories			Frequency(%)/mean ±SD	
Gender	male			71(46.7%)	
	Female	pregnancy	No	60(39.5)	81(53.3%)
			Yes	21(13.8)	
		postpartum	No	64(42.1)	
			Yes	17(11.2)	
Age				39.17±13.5	
Residency	countryside			103(67.8%)	
	urban			49(32.2%)	
AKI	yes			62(40.8%)	
	no			90(59.2%)	
GI bleeding	yes			35(23%)	

	no	117(77%)
Hepatic encephalopathy	Grade 1	26(17.1%)
	Grade 2	19(12.5%)
	Grade 3	59(38.8%)
	Grade 4	48(31.6%)
coagulopathy	INR	5.57±2.55
	APTT(in sec)	59.25±20.85
	PT(in sec)	40.88±13.30
Metabolic abnormalities, liver enzymes, liver synthetic function and liver execretary function	Potassium(meq/l)	3.68±0.48
	Sodium(meq/l)	138.17±5.31
	RBS(mg/dl)	111.09±46.54
	Total bilirubin(mg/dl)	10.81±7.09
	Albumin	2.74±0.82
	BUN	12.29±6.06
	ALT(u/l)	301.4±152.97
	AST(u/l)	345.41±184.51
	ALP(u/l)	124.14±30.05

Platelet count		257000±112395.04
Icterus-encephalopathy interval(in days)		7.65±4.63
Herbal medication exposure	no	112(73.7%)
	Yes	40(26.3%)

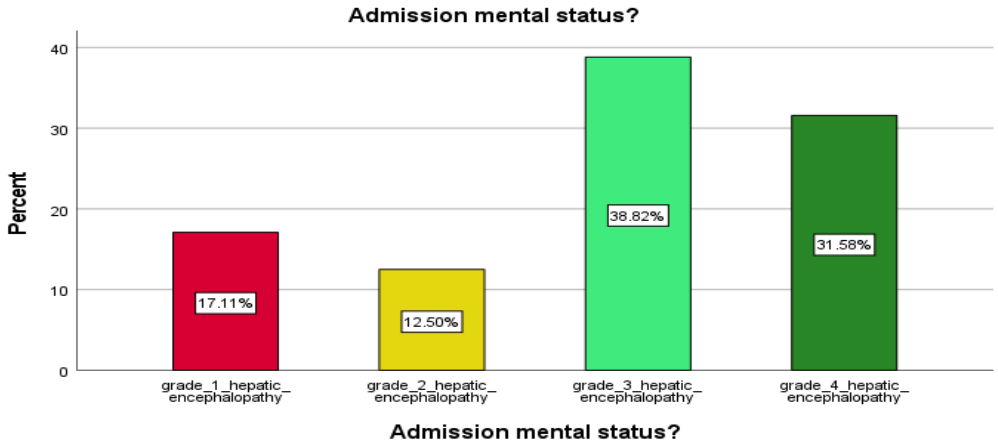


Figure 1hepatic encephalopthy frequency

3.1.2. Magnitude and predictors ofALF mortality (outcome)

Overall, the proportion of acute liver failure mortality among adult medical patients admitted in Tibebegion and FelegeHiwotwas 78.3% (95%CI, 71.7 – 84.9%) and was significantly increased in older patients,in patients with AKI and in patients with higher grade hepatic encephalopathy(grade 3 and 4). it wasalsohigher in females than males(55.5% vs 44.5%) but the difference is not significant(p=0.31).there is non-significant increase in the herbal medication exposure, GI bleeding,being pregnancy and postpartum in non-survivors than survivors.there is significant increase in INR,PT,APTT and total bilirubin level and significant decrease in RBS level in non survivors than survivors. No significant difference between survivors and non-survivorsobserved in the level of AST, ALT, ALP,albumin, Bun and platelet count.Icterus-encephalopathy interval is longer in the non survivor than survivors but not significant (7.90±4.98vs6.75±2.96,p=0.208).

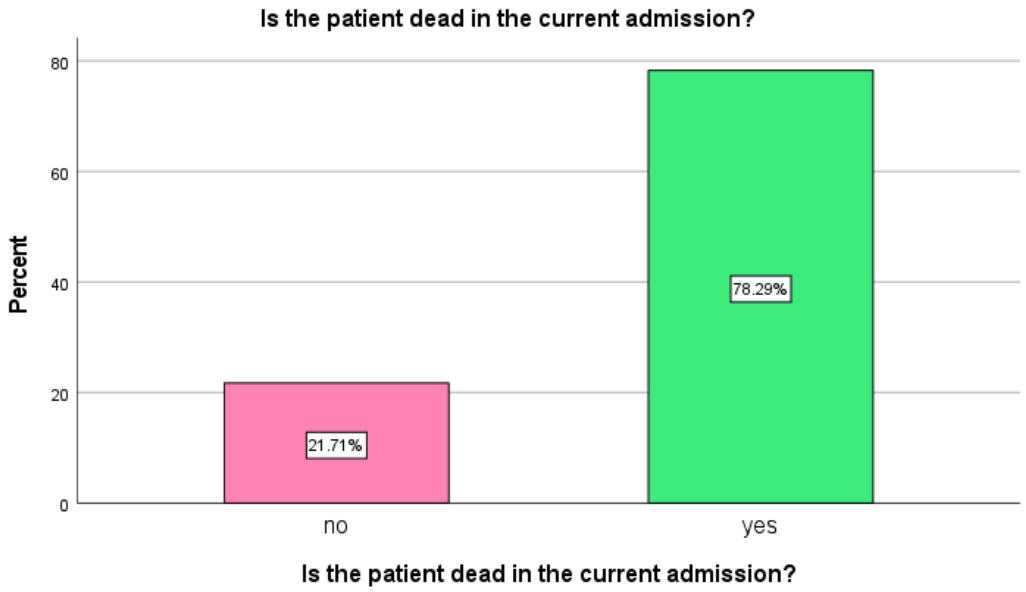


Figure 2ALF mortality frequency

Table 2demographic,clinical and laboratory values in survivorsvs non survivors with univariantanlysis

variable		Survivors(N=33)	Non-survivors(N=119)	P-value
Age(y)		35.03±12.19	40.32±13.67	0.046
Gender, n(%)	male	18(25.4)	53(74.6)	0.308
	female	15(18.5)	66(81.5)	
Residency,n(%)	Countryside	23(22.3)	80(77.7)	0.78
	Urban	10(20.4)	39(79.6)	
Pregnancy	no	10(16.7)	50(83.3)	0.47
	yes	5(23.8)	16(76.2)	

postpartum	no	10(15.9)	53(84.1)	0.252
	yes	5(27.8)	13(72.2)	
Admission mental status	Grade 1 HE	12(46.2)	14(53.8)	0.005
	Grade 2 HE	5(26.3)	14(73.7)	
	Grade 3 HE	7(11.9)	52(88.1)	
	Grade 4 HE	9(18.8)	39(81.3)	
Herbal medication exposure	No	27(24.1%)	85(75.9%)	0.23
	Yes	6(15%)	34(85%)	
AKI	no	27(30)	63(70)	0.003
	yes	6(9.7)	56(90.3)	
GI bleeding	no	28(23.9)	89(76.1)	0.225
	Yes	5(14.3)	30(85.7)	
Coagulopathy	INR	3.6±1.2	6.2±2.5	<0.001
	APTT(in sec)	46.71±11.4	62.72±21.5	<0.001
	PT(in sec)	31.43±7.0	43.5±13.4	<0.001
Metabolic abnormalities	sodium(meq/l)	139.56±4.40	137.79±5.49	0.091

	Potassium(meq/l)	3.76±0.31	3.66±0.52	0.3
	Total bilirubin(mg/dl)	7.37±6.26	11.7±7.03	0.001
	RBS(mg/dl)	133.9±42.94	104.7±45.67	0.001
	Albumin(mg/dl)	2.8±0.82	2.73±0. 82	0.658
	Bun	10.79±5.9	12.71±6.0	0.11
	ALT(u/l)	347.67±146.48	288.57±151.96	0.048
	AST(u/l)	383.76±167.62	334.78±188.20	0.178
	ALP(u/l)	123.76±28.3	124.24±30.6	0.935
Platelet count		277181.8±99167.93	256000±115759.83	0.340
Icterus-encephalopathy interval(in days)		6.75±2.96	7.90±4.98	0.208

3.1.3. Factors associated with acute liver failure mortality

In multivariant analysis age, AKI, GI bleeding, grade 3 or 4 HE, herbal mediation exposure,level of total bilirubin, INR, PT, sodium and RBS level were significantly associated with ALF mortality.As age increases by one year,the odds of ALF mortality increased by 11.9%(AOR=1.119,95%CI,1.034-1.211,p=0.005). Hepatic encephalopathy grades correlated inversely with spontaneous survival. The odds of ALF mortality among individuals with grade 3 and grade 4 hepatic encephalopathy at admission increased 8.2 times(AOR = 8.23, 95%CI,

1.101 – 61.54,p=0.04) and 11 times (AOR = 11.14, 95%CI, 1.23 –100.8,p=0.032),respectively, compared to individuals with grade 1 hepatic encephalopathy. Individuals with AKI had increased odds of ALF mortality 7 times (AOR=7.18,95%CI,1.19-43.2, 0.031), GI bleeding increased odds of ALF mortality 17.6times(AOR=17.67,95%CI,2.23-139.55, 0.006)and herbal medication exposure increased odds of ALF mortality 7.2 times (7.28,95%CI,1.33-39.8,0.022) compared patients without any of these conditions.serum total bilirubin, PT prolongation, INR level, RBS level and serum sodium level at presentation were independent predictors for mortality; odds ratios were 1.12, 1.2,1.99,0.98 and 0.81 respectively.

Table 3bivariant and multivariant logistic regression results

variable		Survivors(N=33)	Non-survivors(N=119)	COR,95%CI,P-value	AOR,95%CI,P-value
Age(y)		35.03±12.19	40.32±13.67	1.03,(1.00-1.06),0.049	**1.119, (1.034-1.211),0.005**
Gender, n(%)	female	15(18.5)	66(81.5)	0.66,(0.308-1.45),0.31	
	male	18(25.4)	53(74.6%)	1	
Residency,n(%)	Countryside	23(22.3)	80(77.7)	1.12,(0.48-2.58),0.78	
	Urban	10(20.4)	39(79.6)	1	
Pregnancy	no	10(16.7)	50(83.3)	1	
	yes	5(23.8)	16(76.2)	0.64,(0.19-2.15),0.471	
Herbal medication exposure	No	27(24.1)	85(75.9)	1	1
	Yes	6(15)	34(85)	1.8,(0.68-4.74),0.235	7.28,(1.33-39.8),0.022

postpartum	no	10(15.9)	53(84.1)	1	
	yes	5(27.8)	13(72.2)	0.49,(0.143-4.147),0.258	
Admission mental status	Grade 1 HE	12(46.2)	14(53.8)	1	1
	Grade 2 HE	5(26.3)	14(73.7)	2.4,(0.66-8.62),0.18	6.25,(0.36-106.1), 0.206
	Grade 3 HE	7(11.9)	52(88.1)	6.36,(2.11-19.19),0.001	**10.7,(1.15-99.8), 0.037**
	Grade 4 HE	9(18.8)	39(81.2)	3.71,(1.28-10.7),0.015	**11.69,(1.21-112.4),0.033**
AKI	no	27(30)	63(70)	1	1
	yes	6(9.7)	56(90.3)	4.0,(1.53-10.39),0.004	**7.18,(1.19-43.2), 0.031**
GI bleeding	no	28(23.9)	89(76.1)	1	1
	Yes	5(14.3)	30(85.7)	1.88,(0.66-5.31),0.23	**17.67,(2.23-139.55), 0.006**
Coagulopathy	INR	3.6±1.2	6.2±2.5	1.79,(1.38-2.31).<0.001	**1.99, (1.12-3.54),0. 015**
	APTT	46.71±11.4	62.72±21.5	1.05,(1.02-1.09),<0.001	0.94,(0.86-1.02), 0.175
	PT	31.43±7.0	43.5±13.4	1.13,(1.07-1.21),<0.001	**1.2,(1.05-1.40), 0.009**
Metabolic abnormalities	sodium (meq/l)	139.56±4.40	137.79±5.49	0.93,(0.86-1.01),0.094	**0.81,(0 .68-0.96), 0.018**
	Potassium(meq/l0	3.76±0.31	3.66±0.52	0.64,(0.28-1.47),0.29	

	Total bilirubin(mg/dl)	7.37±6.26	11.7±7.03	1.1,(1.04-1.20),0.003	**1.12,(1.006-1.26), 0.039**
	RBS(mg/dl)	133.9±42.94	104.7±45.67	0.98,(0.97-0.99),0.003	**0.98,(0 .96-0.99),0.024**
	Albumin(mg/dl)	2.8±0.82	2.73±0. 82	0.89,0.56-1.43),0.655	
	Bun	10.79±5.9	12.71±6.0	1.05,(0.98-1.13),0.11	1.07,(0.92-1.24), 0.34
	ALT	347.67±146.48	288.57±151.96	0.998(0.995-1.0),0.051	0.99,(0.98-1.001), 0.074
	AST	383.76±167.62	334.78±188.20	0.999,(0.997-1.0),0.179	1.004(0.99-1.01), 0.281
	ALP	123.76±28.3	124.24±30.6	1.0,(0.988-1.01),0.93	
Platelet count		277181.8±99167.93	256000±115759.83	1.0,(1.0-1.0),0.33	
Icterus-encephalopathy interval(in days)		6.75±2.96	7.90±4.98	1.06,(0.96-1.17),0.209	0.97,(0 .80-1.18), 0.82

3.2.Discussion

The current study is the first study on ALF mortality in Ethiopia reported to date. the proportion of ALF mortality was 78.3% in patients admitted to Tibebegion and Felegehiwot hospital over 5 years. this proportion is similar to that reported from western(10) and other studies from india (60%-80%)(71) but lower compared with mortality rate in study in US in the pre-transplant era(>90%)(5) .this difference may be due to advancement in supportive care for ALF patients in the post transplant era compared with the pre transplant era. Nevertheless, the proportion of ALF mortality found in our study is high and concerning and still it needs improvement supportive care and availability of liver transplant**.**

This study shows that the mean age of the study population is 39.17 years and most patients are below the mean and 53.7% are women.this implies that ALF affects mainly occurs in the younger population and women in our setup.This is hand in hand with previous studies that reported ALF mainly affects young adults, with a peak age between 35 and 45 years and Women account for approximately 60% of cases(7) and women to men proportion as (52% vs 48%)($p<0.001$)(72).this study also show significant association between age and ALF mortality. As age increases by one year, ALF mortality increases by 11.9%,which is similar with study reported inIndia(73).there was no difference in mortality between the genders (46.3% men vs 53.7% women; p=0.31), which is similar with study report(48% for men vs. 51% for women; p=0.54) in the united states(24).neither being pregnant nor being postpartum associate with ALF mortality which is similar with study conducted inIndia(19)

In our study most(70.4%) of the patients had grade 3 and grade 4 hepatic encephalopathy at admission and significantly associated with ALF mortality compared with grade one hepatic encephalopathy, which is almost similar with study reported in in India(19).this higher proportion of the high grade encephalopathies may be late presentation of the patients in which patients initially develop grade 1 and 2 hepatic encephalopathy progressed to grade 3 and 4 hepatic encephalopathy and significant association of higher grade encephalopathy with ALF mortality may be due to increased grade of hepatic encephalopathy may increase cerebral edema development and increased risk of brain herniation.

In this study renal failure was found to be 40.8% and was significantly associated with ALF mortality, which is similar in incidence with study reported in US(74)but this is higher than that reported in India which showedlower incidence(54 out of 180 or 30%) and no significant association with ALF mortality(19).This discrepancy may be due to in the one hand, in this study all patients who develop renal failure throughout hospitalization course were included in the analysis in contrast to Indian study in which the investigators included patients who develop renal failure only within 48 hours after hospitalization and the other may be difference in supportive care given in the two centers..

In this study GI bleeding is 23% and significantly associated with ALF mortality, which is in contrast to study in India(19) which showed slightly increased incidence(45 out of 180 or 25%)

and no association with ALF mortality. this difference may be due to supportive care given in Indian center may be more advanced than in our set up.

this study show that 26.3% of the patients had herbal medication exposure in the last 3 months.This is similar with burden stated in china mainland which shows 27%(57).Even if not stated in previous studies,this study also shows herbal medication exposure significantly associated with ALF mortality(AOR=7.2,95% CI 1.33-39.8%,P=0.022).this may be due to herbal medication taken by patients may have either idiosyncratic or direct toxic effect to the liver, even if paucity of data.

Most patients(99.3%) in this study have icterus-encephalopathy interval ≤3 weeks, of whom 63.8% had below 8 days. This study also shows that Icterus encephalopathy interval had no significant association with ALF mortality which is similar as stated in New Delhi ,India(46) but in contrast with studies stated in western(7) and India(19)in which 23.3% of the patients had >28 days icterus encephalopathy interval ,have observed significant influence of icterus-encephalopathy duration>8 days on ALF mortality. This difference may be due to difference icterus-encephalopathy interval between the studies,which may be due to difference in etiologies to cause for ALF in the setups(24).

In this study, the mean PT and INR level are 40.88±13.30 and 5.57±2.55,respectively.PT prolongationand increased INR level were significantly associated with ALF mortality.PT prolongation by one second and increased INR level by one value will increase the odds of ALF mortality by 1.2 and 1.99 times,respectively.this is similar to studyreported in India(73). however, APTT prolongation not show influence on mortality in this study. This may be due to PT and INR can measure the intrinsic synthetic function of the liver, so it may associated with severity of liver disease than APTT does.

The mean value of total bilirubin in this study is 10.81±7.09.it is significantly associated with acute liver failure mortality. increase one mg/dl in total bilirubin will increase ALF mortality by 12%.this is similar with study stated in Germany and India(18)(20).this increased association may be due to bilirubin may increase hepatic encephalopathy risk.

Even if no report from previous studies, in this study,the mean value of RBS and serum sodium is 111.09±46.54 and 138.17±5.31, respectively. It shows,that there is significant inverse

association with ALF mortality.when there is one unit decrease serum level of RBS and sodium, there is increased risk of ALF mortalityby 2% and 19% , respectively.this may be due to increased risk of encephalopathy in patients with hypoglycemia and hyponatremia.

Limitation of the study

Generalizability of the results of this study is limited by small sample size and being limited institutions. Due to lack of data on etiology of acute liver failure, etiological analysis was not done in this study and this may need further study since outcomes and the need for transplantation vary widely across different etiologies.

Conclusion

In conclusion, this study is the first study in Ethiopia to date on acute liver failure mortality and its associated factors. The overall proportion of ALF mortality was high in the study institutions. age, higher grade hepatic encephalopathy(grade 3& grade 4),GI bleeding, AKI, coagulopathy, herbal medication exposure,total bilirubin level, serum sodium and blood sugar level was found to be a significant factor associated with risk of acute liver failure mortality. Therefore it is crucial to improve supportive care and combat these factors to improve ALF mortality.

Recommendation

I would like to recommend that supportive care(transfusion support for coagulopathy and GI bleeding, mechanical ventilation, dialysis for renal failure,close monitoring of RBS and serum electrolyes and supplementation when serum value is decreased and coma care)for combating the factors that predict mortality should be improved.

Health education on the side effects of herbal medication should be given to population inorder to avoid it.

Liver transplantation facility should be established to improve acute liver failure mortality because even with intensive supportive care spontaneous survival is low.

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Annex

CHECKLIST

The mortality and its associated factors of acute liver failure in patients admitted to medical ward and ICU in TGSH and FHRH, Bahir Dar, Ethiopia

After ethical approval, the following data were retrieved by reviewing patient's charts.

A. Socio demographic factors

1. Age:
2. Sex:
    a. Male
    b. Female

3.If female , is she pregnant? a)yes b)no

5.if the answer for Q NO.2 female ,is she postpartum?

a)yes b)no

6.Residency a) urban b) rular

B. complications

1. Admission mental status?

a) grade 1 hepatic encephalopathy

b) grade 2 hepatic encephalopathy

c) grade 3 hepatic encephalopathy

d) grade 4 hepatic encephalopathy

2. coagulopathy-how high is the following

i. INR

ii. aPTT(in sec)

iii. PT(in sec)

3. does the patient had AKI ? a) yes b)no

4. does the patient had gastrointestinal bleeding? a) yes b)no

5. metabolic abnormalities

i)liver synthetic function,liverenzymes,platlets and glycemic abnormalities

a. ALT :
b. AST:
c. ALP :
d. Total bilirubin:
e. Albumin:
f. Platelet:
g. RBS(in mg/dl)
h. Serum Potassium(meq/l)
i. Serum sodium(meq/l)

7. icterus-encephalopathy interval/pre-encephalopathy period(in days)……?

8.does the patient had herbal medication exposure in the last 3 months? 1)yes 2) no

9. is the patient dead? 1)yes 2) no

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Approval of Dissertation/thesis for defense

I hereby certify that I have supervised, read, and evaluated this thesis/dissertation titled "mortality and its associted factors of acute liver failure" by AdaneAlemayehu prepared under my guidance. I recommend the thesis/dissertation be submitted for oral defense (mock-viva and viva voce).

Dr Fibrete Wolde	[signature]	11/07/16
1st Advisor's name	Signature	Date
Kebadinew Mulato	[signature]	10/07/16 E.C
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Approval of Dissertation/thesis for defense result

We hereby certify that we have examined this dissertation/thesis entitled “mortality and its associated factors of acute liver failure” byAdaneAlemayehu. We recommend and approve the dissertation/thesis a degree of “ internal medicine specialization”

Board of Examiners

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