Review Article

Acute Liver Failure in Oncology Patients

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Acute Liver Failure (ALF) is a rare entity, seen in previously healthy individuals.[1] It is defined as the presence of coagulopathy (international normalized ratio [INR] >1.5) and hepatic encephalopathy (HE) in a patient with an otherwise healthy liver and with illness of less than 26 weeks. Coagulopathy alone, in the absence of HE, is termed acute liver injury (ALI), carries a much better prognosis. Reported incidence is one to six cases per million per year in the developed countries. Hepatotropic viruses like Hepatitis A and E, and paracetamol overdose are the main cause of ALF. In 14-20% of patients no etiology can be determined, despite systematic investigation.[2] The oncology patients may develop liver failure due to malignancy or its treatment, any surgical or anesthesia-related factors or due to an immunocompromised state. The disease is rapid and aggressive with a high mortality in oncology subset of patients.[3]

Etiology:

The causes of ALF in oncology patients are as follows:

1. Drug-Induced Hepatotoxicity (DIH): United States ALF Group Registry Statistics states that DIH is responsible for more than 50% of cases and is the leading cause of ALF in the USA.

a. Intrinsic Drug-Induced Liver Injury (I-DILI): Acetaminophen is the most causal agent for *I*-DILI. The reactive drug metabolites excessively accumulate causing apoptosis and necrosis of hepatocytes, which is dose-dependent and has a predictable course. Oncology patients are invariably prescribed acetaminophen as a part of their multimodal pain management, they can accidentally or intentionally overdose on it.

b. Idiosyncratic drug-induced liver injury (Is-DILI): Is-DILI follows a more unpredictable course and is independent of the drug dose. It usually starts 7-14 days after the first drug ingestion. The cause is multifactorial, usually a combination of host, drug, and environmental factors. Various drugs implicated are NSAIDs, various antibiotics (Amoxicillin Clavulanate, Sulfamethoxazole-trimethoprim), Amiodarone and Valproate. Also, anti-neoplastic drugs that can cause ALF are tyrosine kinase inhibitors, tumor necrosis factor inhibitors, alpha trypsin inhibitors and methotrexate.[4]

2. Viral hepatitis: The most common viruses associated with ALF are Hepatitis A, B, and E viruses. Intensive chemotherapy creates an immunosuppressive condition leading to reactivation of Hepatitis B virus. Other implicated viruses are Cytomegalovirus, Epstein Barr virus, Herpes Simplex Virus, and Varicella zoster.

3. Auto-immune hepatitis (AIH): AIH typically presents as a chronic necro-inflammatory disease, with acute presentation occurring in 25% of cases leading to massive hepatic necrosis.[5] A flare can occur in an immunocompromised state post chemotherapy or radiotherapy leading to ALF.

4. Post-hepatectomy liver failure (PHLF): ALF can occur when there is deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying function which is characterized by an increase in INR and hyperbilirubinemia on or after postoperative day 5. The '50–50 criteria' predicts a 50% risk of early postoperative mortality if systemic bilirubin rises above 50 µmol/L and prothrombin time decreases to 50% on postoperative day 5. Chemotherapy associated steatohepatitis (CASH) and sinusoidal obstruction syndrome (SOS) are risk factors for PHLF. Preoperative parameters like aspartate aminotransferase to platelet ratio (APRI) and splenic volumetry have been suggested as effective predictors of PHLF especially in the setting of oxaliplatin

induced SOS. Based on the colorectal liver metastasis resection consensus guidelines (2006), the acceptable future remnant liver (FLR) has been stated to be > 20% of Total liver volume (TLV) in normal livers, > 30% in the presence of steatosis and > 40% in the presence of fibrosis/cirrhosis.[6] The peri-operative mortality ranges between 0% (Grade A) to 54% (Grade C). The grading of PHLF and the management is shown in Fig 1 and Table 1.[6]

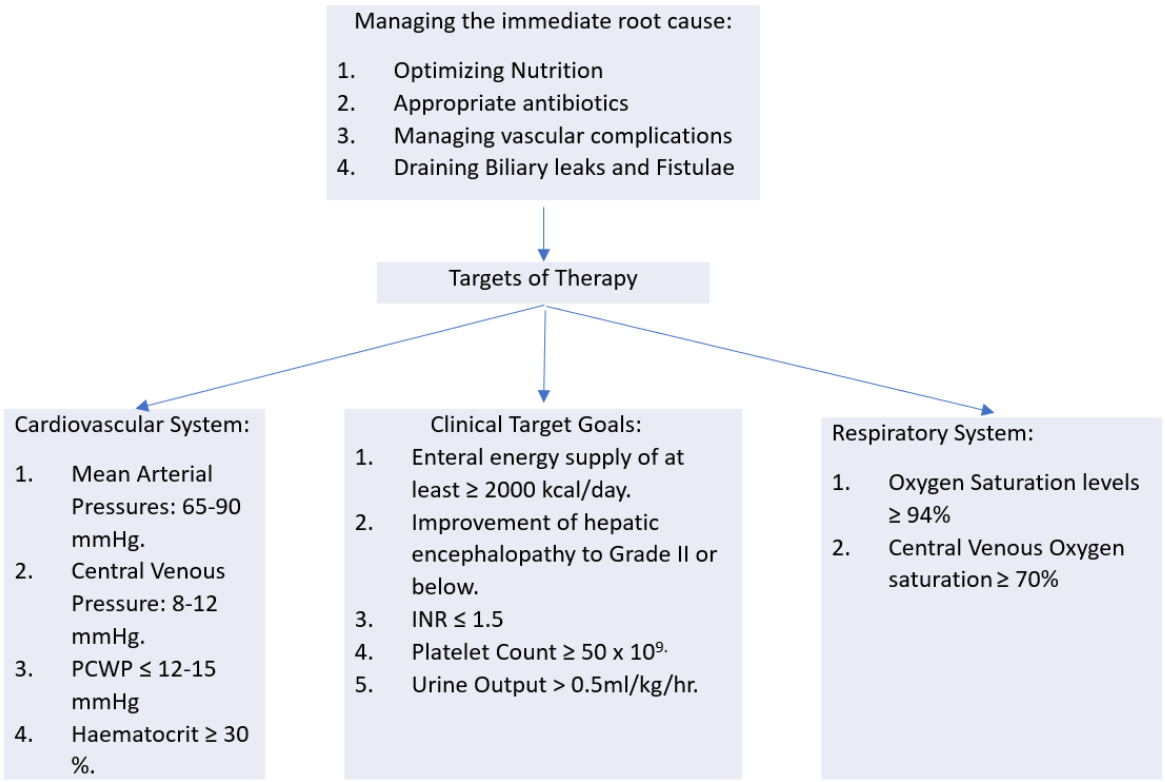


Fig 1. Management protocol for PHLF

TABLE 1 ISGLS definition and grading of PHLF.

GRADE	CLINICAL DESCRIPTION	TREATMENT	DIAGNOSIS	CLINICAL SYMPTOMS	LOCATION FOR CARE
A	Loss of liver function	None	• UO >0.5 ml/kg/h • BUN <150mg/dl • O2 saturation≥90% • INR <1.5	None	Surgical Ward
B	Deviation from the anticipated postoperative course without invasive interventions	Non-invasive: fresh frozen plasma; albumin; Diuretics; non-invasive ventilator support; abdominal ultrasound; CT scan	• UO ≤0.5 ml/kg/h • BUN<150 mg/dl • <90% O2 saturation despite oxygen therapy • INR ≥1.5, <2.0	• Weight Gain • Ascites • Mild Respiratory Insufficiency • Confusion • Encephalopathy	Step down unit or ICU
C	Multi- System failure requiring invasive treatment	Invasive: Intubation and mechanical ventilation; hemodialysis; extracorporeal liver support; salvage hepatectomy; vasopressors; intravenous glucose for hypoglycemia; ICP monitor	• UO ≤0.5 ml/kg/h • BUN ≥150 mg/dl • ≤85% O2 saturation despite oxygen therapy • INR ≥2.0	• Hemodynamic Instability • Respiratory failure • Renal failure • Large-volume ascites • Encephalopathy	ICU

ISGLS, International Study Group of Liver Surgery; PHLS, post hepatectomy liver failure; UO, urine output; BUN, blood urea nitrogen; O2, oxygen.

5. Acute liver failure secondary to malignant infiltration: Even though the liver is the most common location for hematogenous spread of solid tumors, clinically severe hepatic dysfunction is rare with an incidence of 0.44-1.4% in

various studies, but a very high mortality rate of 89%. The most common presentation in these patients is jaundice, followed by abdominal pain and ascites. Most cases are usually due to infiltration by hematological malignancies (Non-Hodgkin lymphoma and Histiocytosis), Cholangiocarcinoma, breast, pancreatic and lung cancer. Non-cancerous conditions such as lymphoma, amyloidosis, or granulomatous diseases can also infiltrate the liver and cause liver failure.[7,8]

6. Radiation induced liver failure (RILD): RILD can range from transient changes in liver enzymes to fulminant hepatic insufficiency manifesting as bleeding predilection, ascites, and HE. This can happen during treatment for liver cancer and other upper abdominal malignant tumors that has poor pharmacological therapeutic options by cell damage via direct energy deposition or reactive free radical generation.[9]

7. Cholangitis: Obstruction of the bile ducts, commonly due to biliary malignancies or infections, can lead to cholangitis and subsequent acute liver failure.

8. Tumor lysis syndrome**:** Rapid breakdown of cancer cells following chemotherapy can release large amounts of intracellular contents, overwhelming the liver's capacity and leading to acute liver failure.

9. Less common causes include ischemia (secondary to shock which could be due to sepsis, intraoperative hemorrhage, or liver congestion due to cardiac failure secondary to chemotherapy), decompensation in Wilson's Disease, Budd-Chiari Syndrome, and pregnancy-related liver failure (HELLP syndrome).

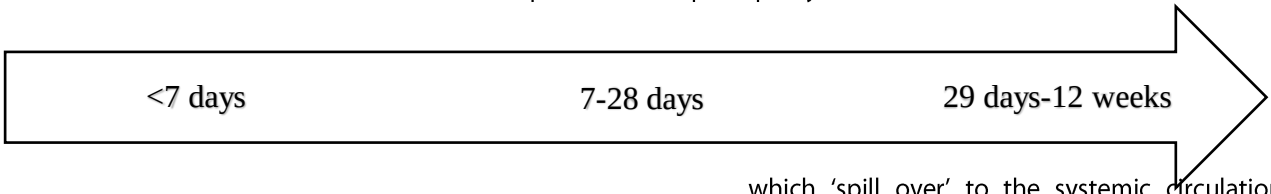
Timeline for diagnosis

The interval between symptom (most commonly jaundice) and HE which is the jaundice-encephalopathy (J-E) interval also indicates the likely causes, complications and prognosis of the liver disease as given in (Table 2).[10]

Table 2. Depending on the J-E interval, O Grady et al[10] have classified Acute liver failure in three groups:

Hyperacute Liver Failure (HALF)	Acute Liver Failure (ALF)	Subacute Liver Failure (SALF)
• Drugs/Toxins • Viral • Pregnancy related • Vascular • Other	• Drugs/Toxins • Viral • Pregnancy related • Vascular • Other	• Drugs/Toxins • Seronegative Hepatitis • Vascular • Other

Timeframe from onset of Jaundice to development of encephalopathy (J-E Interval)



Pathophysiology:

ALF is an innate immune driven disorder, and an immunocompromised oncology patient is at a greater risk to develop it.[11]

In the Initiation phase, there is a massive expansion of hepatic macrophages, followed by a biphasic macrophage response (initial tissue destructive 'M1' response is followed by resolution 'M2' response).

In the Propagation phase, hepatocyte death results in production of large quantities of inflammatory mediators which 'spill over' to the systemic circulation leading to systemic inflammatory response syndrome (SIRS).

Inflammatory mediators cross the blood brain barrier and act synergistically with the elevated ammonia levels leading to HE, a hallmark of ALF. This may progress to astrocyte swelling, intracranial hypertension (ICH) and death due to complex interplay between systemic inflammation, circulating neurotoxins (ammonia in particular), and osmolar derangements such as hyponatremia.

In the Resolution phase, anti-inflammatory mediators like Interleukin 10 (IL 10) and transforming growth factor β (TGF

β), from the inflamed liver oppose the pro-inflammatory response to limit tissue injury. However, spill over of the M2 response to the systemic circulation may predispose the patient to infection and poor outcomes.

Diagnostic approach

i. History and physical findings: Jaundice, coagulopathy, and encephalopathy in patients with no prior liver disease is the sine qua non for diagnosis. However, non-specific symptoms like nausea, vomiting, lethargy, abdominal pain, and a feeling of being generally unwell can also be present. Symptoms will overlap in a patient who has received chemotherapy and/or radiotherapy, but persistent jaundice and encephalopathy should be diligently investigated.

ii. Risk factors: Age > 40 years, chronic alcohol use, female sex, poor nutritional status, pregnancy, chronic hepatitis B, use of acetaminophen for chronic/cancer pain, primary liver malignancy, large liver resections, known liver metastasis and hepatotoxic chemotherapy are risk factors to be considered.[2]

iii. Laboratory findings:

a. Blood tests- Deranged LFTs with hyperbilirubinemia, aminotransferases, and INR are present in all cases. High ammonia levels to >200 µmol/L may predict an increased risk of developing intracranial hypertension (ICH) and should be monitored along with serum lactate. CBC (to look for anemia and thrombocytopenia), urea, creatinine and electrolytes are important baseline investigations.

b. Imaging- Ultrasound and triple phase CT can show changes in liver echogenicity, splenomegaly, ascites, liver surface nodularity, collateral vessel formation, hepatomegaly, or liver atrophy, reversed portal blood flow, and vascular patency. It is important to note that initial studies can be normal and therefore serial images should be considered.[12,13] Infiltrating metastatic tumor has a profound desmoplastic reaction that radiographically resembles cirrhosis and are not identified on radiologic studies. This entity is often called pseudocirrhosis or carcinomatous cirrhosis.[7]

c. Liver biopsy- Early tissue sampling is important as it can clinch the diagnosis in indeterminate cases. Sinusoidal obstruction with micro-infarcts is seen on biopsy in patients presenting with rapid onset of liver failure with high aminotransferases.[7,8]

Specific patterns of derangement may help in etiological diagnosis[3]:

i. *Viral hepatitis*: Aminotransferases in the range of 1000-2000 IU/L with ALT > AST. Viral markers may be positive. A low level of Factor 5 with hepatic encephalopathy may be predictive of mortality, in viral hepatitis.

ii. *Acetaminophen:* Low bilirubin, very high AST > 3500 IU/L and high INR. Check for elevated serum and urine acetaminophen levels. Acidosis in arterial blood gas (ABG) is an important prognostic indicator.

iii. *Acute fatty liver of pregnancy/HELLP syndrome*: Aminotransferases<1000 IU/L, high bilirubin, low platelet count.

iv. *Ischemic hepatic injury*: Very high aminotransferases, 25-250 times of upper limit of normal, increased LDH.

v. *Herpes simplex:* Low bilirubin, increased aminotransferases, and leucopenia.

Management in ICU

All patients with acute liver failure associated with malignancy should be managed by a multidisciplinary team that includes hepatologists, intensivists, and oncologists as the course of clinical deterioration is both rapid and aggressive with a very poor prognosis.[3,14,15]

a) *Role of N-acetylcysteine (NAC):* NAC is a precursor of glutathione and is the antidote to acetaminophen toxicity. The hepatotoxic metabolite of acetaminophen, N-acetyl-*p*-benzoquinone-imine (NAPQI) is inactivated by conjugation with glutathione. NAC is100% hepato-protective when given within 8 hours of paracetamol ingestion. A late presentation should not preclude NAC administration.

b) It may improve hemodynamics and cerebral perfusion pressure and has been found to be beneficial in ALF patients with HE I and II due to non-paracetamol etiologies. It is ineffective in advanced grades of HE.

Dose: 140 mg/kg orally as a loading dose, followed by 70 mg/kg every 4 hours, or 150 mg/kg intravenously over 60 minutes as a loading dose, followed by 12.5 mg/kg/hour over 4 hours, then 6.25 mg/kg/ hour for 18 hours.[3]

c) *Management of cerebral oedema*: Aim is to reduce the raised intracranial pressure (ICP).[3,14,15]

- Nurse patient in a dark and silent area.

- Head elevation of 30 to 45 degrees and avoid sudden and acute head turning.
- Avoid hypercarbia
- Short term hyperventilation during raised ICP and hyperemia (seen by elevated jugular bulb oxygen concentration or $SjvO_2$).
- Maintain a mean arterial blood pressure (MAP) of at least 75 mmHg, to target a cerebral perfusion pressure (CPP) of at least 60 mm Hg.
- Osmotic therapy with 20% mannitol or hypertonic saline. Target serum sodium levels of 145-155 mmol/L.
- Intravenous indomethacin can be tried in whom hyperemia is the main contributor.
- Avoid fever. No proven role of hypothermia currently in this cohort.
- Renal replacement therapy (RRT) can be considered for ammonia clearance even in presence of normal renal functions.[16]
- Sedate and ventilate a patient in grade III/IV encephalopathy. Propofol is routinely chosen for sedation because it may reduce cerebral blood flow.
- Frequent neurological evaluation to look for signs of ICH (e.g., sluggish pupillary reflexes and posturing) should be conducted, 2-3 times per shift.
- Stimulation (including endotracheal suctioning) and pain should be minimized.

d) *Acute kidney injury (AKI)*: Incidence of AKI is around 70% in patients with ALF, and it is associated with a poor prognosis without liver transplant. It is more common with drug-induced ALF. Acidosis, fluid overload, hyperkalemia are indications for RRT. The continuous modes are preferred over intermittent modes of RRT.[16] Avoid nephrotoxic agents and modify drug dosage.

e) *Pulmonary complications*: 30% of ALF patients develop pulmonary complications. Mild Adult respiratory distress syndrome (ARDS) is usually a late presentation in the course of the disease coinciding with liver regeneration or development of sepsis[1]. Lung protective strategies are used for ventilation with careful use of positive end expiratory pressure (PEEP) application in the presence of raised ICP.

e). *Coagulopathy*: The incidence of acute bleeding is low, hence routine correction of INR is not recommended as it obscures an important prognostic marker of liver function. However, post chemotherapy or radiotherapy, point of testing with TEG or ROTEM will help to transfuse the right product in patients who have active bleeding or before any invasive procedure.[3]

f) *Hemodynamics*: Resuscitation should be with normal saline to maintain MAP of 75mmHg and avoid hypotonic intravascular fluids to prevent cerebral oedema. Volume expanding solutions containing dextrose can also be used to prevent hypoglycemia. Send cultures if the patient remains hypotensive despite volume resuscitation and consider vasopressor support (Norepinephrine +/- Vasopressin) to maintain a MAP of at least 75 mmHg or a CPP of 60 mmHg. Due to relative adrenal insufficiency in patients with ALF, hydrocortisone may be considered as an adjunctive measure to reduce systemic vasopressor requirement.[15]

g) *Enteral nutrition*: It should be initiated early and at least 60g of protein per day is advisable. Place a nasogastric tube in all intubated and sedated patients to avoid gagging which can increase ICP. High ammonia levels can be treated with oral and rectal lactulose but avoid repeated enema as it is a stimulus and can raise ICP. Studies have shown a small increase in survival time with lactulose, but there was no difference in the severity of HE or outcome.

h) *Control of sepsis*: High standards of infection control should be maintained to minimize nosocomial sepsis.[1] Impaired hepatic regeneration may lead to a functional immunosuppression with secondary nosocomial sepsis which is a double hit to an oncology patient who is already immunocompromised. Therefore, pre-emptive antibiotics must be administered according to local culture and sensitivity patterns. Prophylactic antimicrobial therapy does not influence survival in ALF patients.[17]

Emerging therapies**:** Extracorporeal liver support (ECLS) devices aim to remove the accumulated ammonia and inflammatory cytokines, improve the pathophysiological features of liver failure, and thus provide a window till native liver recovers or transplant opportunity presents.[18] An ideal ECLS should perform the functions of detoxification, biosynthesis, and regulation. None of the currently available devices actually satisfy all the criteria nor have they proved to be beneficial in oncology patients.

Plasma exchange: High volume plasmapheresis (HVP), defined as exchange of 15% of ideal body weight, has been shown to increase overall survival in ALF, specifically in patients who do not undergo emergency transplantation because of contraindications, and those patients who have deteriorated while waiting for a graft.[19] Data in oncology

patients is lacking but treatment strategy can be extrapolated from the general population.

Liver transplant: Active malignancy is an absolute contraindication for liver transplantation. A transplant is usually reserved for people with primary liver cancer without metastasis, who have 1 tumor that is up to 5 centimeters in diameter, or 2 or 3 tumors that are each less than 3 centimeters in diameter (Milan criteria).

Prognosis:

The outcomes from ALF have improved significantly over the past few decades with better understanding of the disease pathophysiology, early referrals to specialist centers equipped with a transplantation facility, better organ system support in ICU, and the availability of emergency liver transplant (LT)[15]. Identifying aetiology helps in determining prognosis and initiate aetiology specific therapies wherever possible.

Mode of death has also changed over time with ICH replaced by sepsis and multiple organ failure as the leading cause of death.[3]

The different systems currently used to assess prognosis in patients with ALF worldwide utilize admission laboratory measures (coagulopathy of highest weight) and recognize the development of HE and advanced age as markers of poor prognosis. One of the oldest and most utilized tools which has high specificity and low sensitivity is the King's College Criteria (KCC). The model of end-stage liver disease (MELD) score, widely used for liver prioritization/allocation in chronic liver disease, has been investigated in ALF with similar performance to that of the KCC.[20] Other useful prognostic criteria include Clichy criteria (presence of HE along with a factor V level lower than 20% to 30% of normal, MELD score higher than 30, and Acute Physiology and Chronic Health Evaluation (APACHE) II score higher than 15).

The need for individualized, dynamic assessments (ALFED and SOFA score) as opposed to historically static ones at presentation is now being advocated[21] and may predict the prognosis better in oncology patients where ALF is more aggressive, and the disease course is rapid.

Circulating blood levels of caspase-cleaved (higher level of caspase activation is seen in spontaneous recovery) and uncleaved cytokeratin K18 (referred to as CK18), an apoptosis cell death marker, are biomarkers that have shown promise in prediction of outcome with ALF. Circulating levels of these biomarkers with standard blood measures of coagulation and renal function demonstrated superior sensitivity and specificity to KCC in predicting ALF outcome, although further studies are needed. HLA-DR monocyte expression has been identified as a potential biomarker of ALF severity and outcome in acetaminophen-related ALF.[20]

ALF is an acute severe life-threatening condition from diverse etiologies that carries a high mortality but is potentially reversible. Oncology patients have symptom overlap, with a rapid and aggressive progression, and poor outcome. Associated multisystem organ dysfunction and grade III/IV hepatic encephalopathy with chance for progression to brainstem herniation mandates prompt recognition and intensive care treatment.

The outcomes have improved significantly with a better understanding of the disease, improvements in intensive care and increased availability of transplants in the general population. Intensive care is needed to bridge ALF patients to transplant in primary liver cancer patients who meet the Milan criteria or with the hope of spontaneous regeneration in other malignancies or PHLF. Although chemotherapeutic agents have a role, their utility is extremely limited as the patients with impaired hepatic function are often not suitable candidates for chemotherapy given concomitant immunosuppressed states, infection and multiorgan failure.

Conflict of interest: Nil

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