Circulating biomarkers predictive of mortality in patients undergoing liver transplantation for hepatocellular carcinoma

Leonardo Lorente

ABSTRACT

There are different macromorphological factors obtained before liver transplantation (LT) to predict the prognosis of patients with hepatocellular carcinoma (HCC) undergoing LT. In addition, the use of blood biomarkers could help to improve the prognostic prediction of these patients. Blood levels of alpha-fetoprotein (AFP) are the first and most studied blood biomarkers of prognosis of HCC patients undergoing LT. Moreover, interesting data on new or already known circulating biomarkers predictive of mortality in patients with HCC undergoing LT have been published in recent years. The aim of this review is to summarize the evidence for circulating biomarkers predicting mortality of HCC patients undergoing LT. A higher mortality rate has been found with high blood levels of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immunoinflammation index (SII), C-reactive protein (CRP), albumin bilirubin score (ALBI), de-gamma-carboxy prothrombin (DCP), lactate dehydrogenase (LDH), gamma glutamyl transeptidase (GGT), fibrinogen, vascular endothelial growth factor (VEGF), homocysteine, Golgi protein 73 (GP73), substance P, soluble CD40 ligand (sCD40L), caspase cleaved cytokeratin (CCCK)-18, caspase-3, malondialdehyde, oxidized guanine species (OGS) and soluble Fas ligand (sFasL). A higher mortality rate has been observed with low blood levels of lymphocyte-to-monocyte ratio (LMR), PD-L1, Galectin-9, total antioxidant capacity (TAC) and melatonin. Furthermore, some studies with small sample sizes have been published associating blood levels of metabolites and microRNAs (MIR) with the prognosis of HCC patients undergoing LT. Therefore, further investigations are needed to determine the potential usefulness of these blood biomarkers in predicting mortality of HCC patients undergoing LT.

Key words: hepatocellular carcinoma, liver transplantation, biomarkers, outcome, survival

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and causes a large number of cancer-related deaths.\(^1\) Liver transplantation (LT) is the treatment of choice in some patients with HCC, as liver failure is treated and the tumor is removed.\(^6\)–\(^10\)

There are different macromorphological factors obtained before HT to predict the prognosis of HCC patients undergoing HT, such as Milan criteria, tumor size, degree of differentiation, number of tumors, infiltration, hepatic microvascular invasion and hepatic macrovascular invasion\(^11\)\(^–\)\(^15\). In addition, the use of blood biomarkers could help to improve the prognostic prediction of these patients. Blood levels of alpha-fetoprotein (AFP) are the first and most studied prognostic blood biomarkers of HCC patients undergoing LT.\(^16\)\(^,\)\(^17\) In addition, interesting data on new or already known circulating biomarkers predictive of...
mortality in HCC patients undergoing CT have been published in recent years. The aim of this review is to summarize the evidence for circulating biomarkers predicting mortality in HCC patients undergoing CT (see Table 1).

BIOMARKERS

**Alpha-fetoprotein**

Blood levels of alpha-fetoprotein (AFP), glycoprotein increase with different AFP-producing tumors, such as testicular or ovarian tumors or HCC. High blood levels of AFP have been associated with increased mortality and recurrence of HCC in patients undergoing LT for HCC.

In a review published by Hakeem *et al.* in 2012, 13 observational studies with 12,159 HCC patients undergoing LT for HCC were included to determine the role of circulating AFP levels obtained prior to LT in predicting survival and HCC recurrence. A valid meta-analysis of all these studies was not possible due to the large heterogeneity in the way blood AFP levels were reported. Nine of the 13 studies reported serum AFP levels before LT and survival; however, 4 studies reported absolute serum AFP values, and 5 studies reported serum AFP cut-off levels (and the cut-off values reported in the different studies were very heterogeneous). Most studies found an increased risk of death with elevated pre-LT serum AFP levels and that serum AFP cut-off levels above 1000 ng/mL could predict an increased risk of death. Of the 13 studies that reported data on pre-LT serum AFP values and recurrence, 10 studies found an association between high AFP levels and increased HCC recurrence.

In 2016, a review and meta-analysis by Pommergaard *et al.* examined the potential role of different biomarkers in predicting HCC recurrence in patients undergoing LT. The review included a total of 49 studies with 13,693 patients reporting data on serum AFP levels prior to LT and HCC recurrence. As in the previous review, it was not possible to perform a valid meta-analysis with all these studies due to the large heterogeneity in AFP definitions and cut-off values. However, a meta-analysis was performed that included 17 of 49 studies with AFP cut-off values above 400 ng/mL (although the cut-off values reported in the different studies were very heterogeneous) and found an association between elevated pre-LT serum AFP levels and increased risk of HCC recurrence [hazard ratio (HR): 2.69; 95% confidence interval (CI): 2.08 to 3.47].

**Circulating blood cell counts and ratios**

Different circulating blood cell count ratios, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immunoinflammation index (SII), have been used as biomarkers to assess systemic inflammatory responses and have been studied to establish the prognosis of HCC patients undergoing LT.

In a meta-analysis published by Zheng *et al.* in 2017 involving patients with HCC, the possible associations between NLR and PLR before receiving different treatments (LT, transarterial chemoembolization, radiofrequency ablation or chemotherapy) and overall survival and HCC recurrence were studied. The authors found an association between higher NLR and higher mortality rate with all treatments combined (HR: 1.54, 95% CI: 1.34 to 1.76, *P* < 0.001) in an analysis of 19 studies and 4,889 patients and an association between higher PLR and higher mortality rate with all treatments combined (HR: 1.63, 95% CI: 1.34 to 1.98, *P* < 0.001) in an analysis of 18 studies and 4,867 patients. The authors found an association between higher NLR and higher HCC recurrence rate with all combination therapies (HR: 1.45; 95% CI: 1.16 to 1.82; *P* = 0.001) in an analysis of 11 studies and 2,792 patients and an association between higher PLR and higher HCC recurrence rate with all combination therapies (HR: 1.52; 95% CI: 1.21 to 1.91; *P* < 0.001) in an analysis of 13 studies and 3,308 patients. In the specific analysis of 2 studies with 371 HCC patients undergoing LT, an association was found between a higher NLR and a higher mortality rate (HR: 3.12; 95% CI: 1.62 to 6.00). In the specific analysis of 2 studies with 524 HCC patients undergoing LT, an association was observed between higher NLR and higher mortality rate (HR: 2.28; 95% CI: 1.63 to 3.18). In the specific analysis of 3 studies with 714 patients with HCC undergoing CT, an association was observed between a higher PLR and a higher HCC recurrence rate (HR: 1.83; 95% CI: 1.31 to 2.56). However, in the specific analysis of patients with HCC undergoing LT, no association between LPL and HCC recurrence was observed.

A meta-analysis published in 2016 by Sun *et al.* including 1,687 patients from 10 studies found an association between elevated pre-LT NLR and increased risk of mortality (HR: 2.71, 95% CI: 1.91 to 3.83) in patients with HCC undergoing LT. A meta-analysis published in 2018 by Xu *et al.* which included 1,936 patients from 13 studies, also found this association between elevated pre-LT NLR and increased mortality risk in patients with HCC undergoing LT (HR: 2.22; 95% CI: 1.34 to 3.68).

A low MRL was associated with mortality in 216 patients with HCC undergoing LT. SII is calculated by multiplying the platelet count by the neutrophil count and dividing by the lymphocyte count. In a study of 189 patients and in another study of 150 patients, a significant association between low MRL and increased mortality was found.
<table>
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elevated SII was associated with mortality in patients with HCC undergoing LT; moreover, the area under the curve for predicting mortality was higher for SII than for PLR, NLR, and MLR.\(^{[23]}\)

**C-reactive protein**

C-reactive protein (CRP) is synthesized by hepatocytes in response to inflammatory processes and subsequently released into the bloodstream. High blood CRP levels have been associated with an increased risk of HCC recurrence in patients undergoing CT.\(^{[24–26]}\) In addition, high blood CRP levels have been associated with an increased risk of mortality in patients with HCC undergoing LT (and those studies included 85, 96, and 119 patients, respectively).\(^{[24,25,27]}\)

**Albumin-bilirubin bilirubin score**

A study of 123 patients\(^{[28]}\) and another study of 81 patients\(^{[29]}\) showed an association between an high blood albumin-bilirubin bilirubin (ALBI) score and mortality in patients with HCC undergoing LT.

**De-gamma-carboxy-prothrombin**

De-gamma-carboxy-prothrombin (DCP) is a non-functional form of prothrombin produced by the liver. The normal liver converts the glutamic acid residues of the N-terminal portion of prothrombin by carboxylation to gamma-carboxylglutamic acid residues before their release into the peripheral blood. In many HCC cells, the vitamin K-dependent carboxylase that produces this carboxylation is absent; therefore, abnormal prothrombin is secreted.

High blood levels of DCP have been associated with an increased risk of HCC recurrence in patients with HCC undergoing LT.\(^{[30–33]}\) In addition, high blood DCP levels were associated with mortality in patients with HCC undergoing LT in a study of 213 patients\(^{[34]}\) and in another study of 246 patients.\(^{[35]}\)

**Lactate dehydrogenase**

A study of 155 HCC patients undergoing LT\(^{[36]}\) has found an association between high blood lactate dehydrogenase (LDH) and mortality.

**Gamma glutamyl transpeptidase**

A study of 130 patients\(^{[37]}\) and another study of 285 patients\(^{[38]}\) showed an association between high blood gamma glutamyl transpeptidase (GGT) levels and mortality in patients with HCC undergoing LT.

**Fibrinogen**

High blood fibrinogen levels were associated with mortality in patients with HCC undergoing LT in one study of 41 patients\(^{[39]}\) and in another study of 130 patients.\(^{[40]}\)

**Vascular endothelial growth factor**

In a meta-analysis published in 2013 by Zhang et al., which included 11 studies and 782 HCC patients undergoing LT for HCC, an association was found between high blood vascular endothelial growth factor (VEGF) levels obtained before LT and mortality risk (HR: 1.88; 95% CI: 1.46 to 2.3).\(^{[41]}\) After the publication of this meta-analysis, two more studies were published, reporting that high blood VEGF levels obtained before LT in patients with HCC are associated with mortality risk (and these studies included 164 and 180 patients, respectively).\(^{[42,43]}\)

**Homocysteine**

In a study of 161 patients with HCC undergoing LT, high blood homocysteine levels were associated with an increased risk of mortality.\(^{[44]}\)

**Golgi protein 73**

Golgi protein 73 (GP73) is a type II Golgi membrane protein expressed primarily in biliary epithelial cells. GP73 expression is increased in various liver diseases, such as HCC. An association between high blood levels of GP73 and mortality was observed in 60 patients with HCC undergoing HT.\(^{[45]}\)

**PD-L1 and Galectin-9**

PD-L1 and Galectin-9 are two ligands with modulatory effects on T-cell function. When PD-L1 ligand binds to its receptor PD-1 or when Galectin-9 ligand binds to its receptor TIM-3, a negative signal appears on T-cells inhibiting their activation. HCC cells express PD-L1, PD-1, Galectin-9 and TIM-3, and the interaction of these ligands with their receptor impairs the function of effector T-cells in HCC. The authors had previously observed that higher expression levels of PD-L1 and Galectin-9 in HCC are associated with poor survival. Blood levels of the soluble forms of PD-L1 and Galectin-9 have been found in different types of cancer. In a study of 81 patients undergoing resection of hepatocarcinoma or LT for HCC, low blood levels of PD-L1 or galectin-9 were associated with an increased risk of mortality.\(^{[46]}\)

**Metabolomics**

In a study with 122 patients, high blood levels of three
metabolites (phosphatidylcholine 16:0/P-18:1, phosphatidylcholine 18:2/OH-16:0, and nutriacolic acid) obtained before LT in patients with HCC were associated with an increased rate of HCC recurrence.\(^{[57]}\)

**Cell-free circulating RNA or microRNA molecules**

MicroRNA molecules (MIRs) released from cells by necrosis or apoptosis may appear in the blood. Some studies with small sample sizes have determined the blood levels of different MIRs, which have been associated with the prognosis of HCC patients undergoing LT. High blood levels of miR-92b have been found in 93 patients with HCC compared with control subjects and at 1 month after undergoing LT for HCC in patients with HCC recurrence.\(^{[48]}\) Low blood levels of miR-718 obtained in 59 patients prior to LT for HCC have been associated with HCC recurrence.\(^{[49]}\) High miR-1246 blood levels obtained in the early phase after LT for HCC (2 hours after portal vein reperfusion) in 12 patients have been associated with higher rates of HCC recurrence and mortality.\(^{[50]}\) High blood levels of miR-193a-5p have been found in 41 patients with HCC compared to control subjects and before surgical treatment (tumor resection or LT) for HCC in patients with a higher mortality rate.\(^{[51]}\) High blood levels of some MIRs (miR-130b-5p and miR-21-5p) were observed in 46 HCC patients and in patients with poor prognosis HCC; moreover, in vitro, tumors treated with miR-130b or miR-21 inhibitors showed significantly less growth.\(^{[52]}\)

A study of 193 patients with HCC undergoing LT showed that those with positive plasma microRNA panel status (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a and miR-801) prior to LT had a higher rate of tumor recurrence.\(^{[53]}\)

**Matrix metalloproteinase (MMP)-9**

Matrix metalloproteinases (MMPs) are a group of endoproteases involved in the degradation and remodeling of the extracellular matrix.\(^{[54]}\) MMP activity is modulated by different tissue inhibitors of matrix metalloproteinases (TIMPs). MMPs are implicated in physiological functions such as morphogenesis and tissue remodeling and play roles in various diseases such as atherosclerosis, arthritis, tumors, sepsis, stroke and trauma.

In a study of 33 patients with HCC or cirrhosis without HCC undergoing LT, high serum levels of MMP-9 one week after LT were associated with an increased rate of LT rejection.\(^{[55]}\) On the other hand, in another study of 134 HCC patients undergoing different treatments (LT, curative resection, thermoablation or transarterial chemoembolization), low serum levels of MMP-9 and high serum levels of TIMP-1 were found to be associated with a higher mortality rate; however, patients undergoing LT were not specifically examined due to the small sample size of this group of patients.\(^{[56]}\) Therefore, further investigations are needed to determine the possible prognostic role of blood MMP-9 levels in HCC patients undergoing LT.

**Substance P**

Tachykinins are distributed throughout the respiratory system, central and peripheral nervous systems, intestine and urinary system. They are involved in various biological processes, such as transmission of nociceptive responses, inflammation, vasodilation, smooth muscle contraction, salivary secretion and airway contraction.\(^{[57]}\)

Substance P, a member of the tachykinin family, has been associated with diseases such as asthma, inflammatory bowel disease, and diseases of the central and peripheral nervous systems.

High blood levels of substance P have been found in patients with liver disease, especially in patients with severe liver disease.\(^{[58,59]}\) In a study performed by our team with 142 patients with HCC undergoing LT, higher levels of substance P in blood before LT were observed in patients who died during the first year of LT than in survivors at one year.\(^{[60]}\) These findings are consistent with those of other studies reporting an association between high blood levels of substance P and increased risk of mortality in patients with head injury, ischemic stroke or cerebral hemorrhage.\(^{[61]}\)

The use of agents that reduce substance P activity in animal models of traumatic brain injury or ischemic stroke has reduced the inflammatory process and edema formation. Therefore, it would be interesting to explore the potential benefits of administering agents that reduce substance P activity in HCC patients undergoing LT.

**Soluble CD40 ligand**

CD40 ligand (CD40L) is a protein belonging to the tumor necrosis factor superfamily (TNFSF) group of ligands, and its receptor CD40 belongs to the tumor necrosis factor receptor superfamily (TNFRSF).\(^{[62]}\) CD40L is mainly restored on platelets, but also on lymphocytes, monocytes, endothelial cells, smooth muscle cells and microglia. CD40L is released into the blood in soluble form (sCD40L). CD40L exhibits proinflammatory and prothrombotic effects when bound to CD40.

An association was found between high blood levels of sCD40L and poor prognosis in patients with HCC.\(^{[63]}\) In a study by our team with 139 patients with HCC undergoing LT, higher levels of sCD40L in blood before LT were observed in patients who died during the first year of LT than in survivors at 1 year.\(^{[64]}\) These results
are consistent with those of other studies reporting an association between elevated sCD40L blood levels and an increased risk of mortality in patients with acute coronary syndrome,[91] sepsis,[92] traumatic brain injury,[93] or cerebral infarction.[94]

A reduction in CD40 expression was observed when cerebral vascular endothelial cells were preincubated with statins.[78] In addition, the use of statins in rats with traumatic brain injury decreased cerebral edema and intravascular thrombosis and impaired cognitive and motor functions.[79] In addition, a reduction in sCD40L blood levels has been observed in patients treated with statins.[77–79] A meta-analysis of patients with ischemic stroke found a lower risk of death and less neurological deterioration in patients treated with statins.[80] Therefore, it would be interesting to explore the potential benefits of administering agents that reduce sCD40L levels in patients with HCC undergoing LT.

**Caspase-cleaved cytokeratin-18**

Cytokeratin-18 is the major intermediate filament protein in the liver, epithelial cells and parenchymal cells. Cytokeratin-18 is cleaved by caspases during hepatocyte apoptosis and released into the blood.[81]

An association was found between high blood levels of caspase-cleaved cytokeratin (CCCK)-18 and mortality in patients with HCC.[82] In a study performed by our team with 135 HCC patients undergoing LT, higher levels of CCCK-18 in blood before LT were observed in patients who died during the first year of LT than in survivors at 1 year.[83] These findings are consistent with those of other studies reporting an association between high blood CCCK-18 levels and poor prognosis in patients with various tumor diseases,[84–88] sepsis,[89] cerebral infarction,[90] cerebral hemorrhage[91] or traumatic brain injury.[92]

The use of different agents decreased apoptosis and improved prognosis in animal models of sepsis,[93] traumatic brain injury,[94] cerebral infarction[95] and cerebral hemorrhage.[96] Therefore, it would be interesting to explore the potential benefits of administering agents that reduce apoptosis in HCC patients undergoing LT.

**Caspase-3**

Caspase-3 is the main caspase executioner that produces cellular changes during apoptosis.[97] There are two main pathways (extrinsic and intrinsic) for cell death by apoptosis. The extrinsic apoptotic pathway is activated when a TNFRSF member binds to its ligand (TNFSF), generating a death signal responsible for the activation of caspase-8. The intrinsic apoptotic pathway is activated when oxygen free radicals, proinflammatory cytokines or genetic mutations cause the release of cytochrome c from the mitochondria into the cytosol, generating an apoptosome responsible for caspase-9 activation. Subsequently, both apoptotic pathways, due to caspase-8 and caspase-9 activation, lead to caspase-3 activation, resulting in cell death.

A higher degree of hepatic apoptosis and hepatic caspase-3 activity has been found in patients with different liver diseases (chronic alcoholic hepatitis or chronic hepatitis C virus infection).[98–100] In a study performed by our team with 145 patients with HCC undergoing LT, higher levels of caspase-3 in blood before LT were found in patients who died during the first year of LT than in survivors at 1 year.[101] These findings are in line with those of other studies reporting an association between high blood caspase-3 levels and an increased risk of mortality in patients with sepsis,[102] cerebral infarction,[103] traumatic brain injury,[104] or cerebral hemorrhage.[105]

The use of different agents decreased apoptosis and improved prognosis in animal models of sepsis,[106] traumatic brain injury,[107] cerebral infarction[108] and cerebral hemorrhage.[109] Therefore, it might be interesting to explore the potential benefits of administering caspase-3-lowering agents in HCC patients undergoing LT.

**Malondialdehyde**

Malondialdehyde is a low molecular weight aldehyde and is one of the end products that appear during lipid peroxidation of cell membrane phospholipids by free radical action. Malondialdehyde is released into the extracellular space and can reach the bloodstream.[110]

High blood levels of malondialdehyde have been reported in patients with HCC compared to control subjects.[111–113] In a study performed by our team with 127 patients with HCC undergoing LT, higher levels of malondialdehyde in blood before LT were observed in patients who died during the first year of LT than in survivors at 1 year.[114] These findings are in line with those of other studies reporting an association between high blood malondialdehyde levels and increased risk of mortality in patients with sepsis,[115] traumatic brain injury,[116] cerebral infarcts[117] or spontaneous intracerebral hemorrhage.[118]

Melatonin administration (with antioxidant effects) has been associated with improved liver function in animals with different liver diseases[119–123] and in patients with HCC.[124–127] Therefore, it would be interesting to explore the possible benefits of the administration of antioxidant agents to reduce oxidative damage in HCC patients undergoing LT.
**Total antioxidant capacity**

Total antioxidant capacity (TAC) provides information on the overall antioxidant status that protects us from free radicals. Higher blood levels of malondialdehyde have been reported in patients with HCC than in control subjects. In a study performed by our team with 142 patients with HCC undergoing LT, lower pre-LT blood TAC levels were observed in patients who died during the first year of LT than in survivors at 1 year. Furthermore, we found a negative association between serum TAC levels and malondialdehyde; thus, non-surviving patients showed lower antioxidant status and higher lipid peroxidation. As mentioned above, melatonin administration (with antioxidant effects) has been associated with improved liver function in animals with different liver diseases and in patients with HCC. Therefore, it would be interesting to explore the possible benefits of administration of antioxidant agents to increase antioxidant status in HCC patients undergoing HT.

**Melatonin**

Melatonin is released mainly by the pineal gland with a circadian rhythm (high production during the night and low production during the day) and by other organs (bone marrow, gastrointestinal tract, lymphocytes and thymus) without a circadian rhythm. Melatonin, in addition to playing an important role in sleep regulation, also has anti-inflammatory, anti-apoptotic and antioxidant effects.

In a study performed by our team with 145 HCC patients undergoing LT, lower pre-LT blood melatonin levels were observed in patients who died during the first year of LT than in survivors at 1 year. Furthermore, we found a positive association between serum melatonin levels and TAC and a negative association between serum melatonin levels and malondialdehyde; thus, non-surviving patients showed lower melatonin levels, lower antioxidant status and higher lipid peroxidation. As mentioned above, melatonin administration in animals subjected to hepatic ischemia/reperfusion and injection of a HCC-inducing agent or injection of hepatoma cells was associated with less impairment of liver function, less oxidative damage, and a higher survival rate. Furthermore, melatonin administration in patients undergoing hepatectomy or in patients with unresectable HCC was associated with less deterioration of liver function. Therefore, it would be interesting to explore the potential benefits of melatonin administration in HCC patients undergoing HT.

**Oxidized guanine species**

Higher blood levels of oxidative damage products of nucleic acids have been found in patients with cardiovascular disease, heart failure and periodontal disease than in healthy subjects and in patients who died after sepsis, traumatic brain injury, cerebral infarction or spontaneous intracerebral hemorrhage. Reactive oxygen species can damage deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Guanine is one of the nucleobases present in DNA and RNA. The three oxidized guanine species (OGS) are 8-hydroxy-2′-deoxyguanosine (8-OHdG) from DNA, 8-hydroxyguanosine (8-OHGu) from DNA or RNA, and 8-hydroxyguanosine (8-OHG) from RNA. Greater oxidative DNA damage (assessed by 8-OHdG concentration in liver biopsy samples) has been found in patients with chronic liver disease than in healthy subjects. These findings are in line with those of other studies reporting an association between high blood OGS levels and an increased risk of mortality in patients with sepsis, traumatic brain injury, cerebral infarction or spontaneous intracerebral hemorrhage. Therefore, it would be interesting to explore the potential benefits of administering antioxidant agents to reduce oxidative damage to nucleic acids in HCC patients undergoing LT.

**Soluble Fas ligand**

Soluble Fas ligand (sFasL) is one of the main ligands that activate apoptosis by extrinsic pathways; upon binding of FasL to Fas (its receptor), a death signal appears that will activate caspase 8. Subsequently, caspase 8 will activate caspase 3, causing cell death. Subsequently, caspase 8 will activate caspase 3, causing cell death.

A higher lymphocyte expression of FasL has been found in patients with acute LT rejection than in patients without rejection. In a study by our team of 127 patients with HCC undergoing LT, higher pre-LT blood levels of sFasL were observed in patients who died during the first year of LT than in survivors at 1 year. These findings are in line with those of other studies reporting an association between high blood sFasL levels and increased risk of mortality in patients with sepsis, head injury or cerebral hemorrhage. The administration of different agents that reduce Fas/FasL activity in animal models of ischemia/reperfusion liver injury has reduced hepatocyte apoptosis and increased animal survival. Therefore, it might be interesting to explore the potential benefits of administering agents that reduce the activity of the Fas/FasL...
system in HCC patients undergoing LT.

**CONCLUSION**

A higher mortality rate has been observed in HCC patients undergoing LT with high blood levels of AFP, NLR, PLR, SII, CRP, ALBI score, DCP, LDH, GGT, fibrinogen, VEGF, homocysteine, GP73, substance P, sCD40L, CCCK-18, caspase-3, malondialdehyde, OGS, and sFasL. A higher mortality rate has been observed in HCC patients undergoing LT with low blood levels of MRL, PD-L1, galectin-9, TAC and melatonin. In addition, some studies with small sample sizes have been published associating blood levels of metabolites and MIR and prognosis of HCC patients undergoing LT.

**DECLARATIONS**

**Conflicts of interest**

The author has no financial or other conflicts of interest to declare related to the submitted manuscript.

**Data sharing statement**

No additional data is available.

**REFERENCES**


