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REVIEW

New prognostic biomarkers of mortality in patients undergoing liver transplantation for hepatocellular carcinoma

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Abstract

The outcome prediction of hepatocellular carcinoma (HCC) patients undergoing liver transplantation (LT) was classically established using various macromorphological factors and serum alpha-fetoprotein levels prior to LT. However, other biomarkers have recently been reported to be associated with the prognosis of HCC patients undergoing to LT. This review summarizes clinical data on these new biomarkers. High blood levels of malondialdehyde, total antioxidant capacity, caspase-cleaved cytokeratin-18, soluble CD40 ligand, substance P, C-reactive protein, and vascular endothelial growth factor, increased neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in blood, high peripheral blood expression of human telomerase reverse transcriptase messenger ribonucleic acid, and high HCC expression of dickkopf-1 have recently been associated with decreased survival rates. In addition, high blood levels of des-gamma-carboxy prothrombin, and high HCC expression of glypican-3, E-cadherin and beta-catenin have been associated with increased HCC recurrence. Additional research is necessary to establish the prognostic role of these biomarkers in HCC prior to LT. Furthermore, some of these biomarkers are also interesting because their potential modulation could help to create new research lines for improving the outcomes of those patients.

Key words: Liver transplantation; Hepatocellular carcinoma; Biomarkers; Outcome; Survival; Recurrence; Genomic

Core tip: The outcome of liver transplantation (LT) for hepatocellular carcinoma (HCC) patients are generally predicted using various macromorphological factors and serum alpha-fetoprotein levels prior to LT. However, other biomarkers have recently been reported to be associated with the prognosis of HCC patients undergoing LT. Furthermore, some of these biomarkers are also interesting because their potential modulation could help to create new research lines for improving

the outcomes of those patients. This review summarizes clinical data on those new biomarkers.

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most frequent primary liver malignancy, is one of the most common malignancies and causes of cancer-related deaths[1-3]. In liver transplantation (LT), the primary tumor is removed, and liver failure is treated. Therefore, LT is considered the treatment of choice for some HCC patients[1-11].

Various macromorphological factors assessed prior to LT have been classically used to predict the outcome of HCC patients undergoing LT. These factors include the tumor size, tumor number, degree of differentiation, hepatic microvascular invasion, hepatic macrovascular invasion, being outside the Milan criteria and infiltration[1-11].

However, establishing biomarkers to be assessed prior to LT could strengthen the predictions of prognoses for HCC patients undergoing LT. Currently, the most commonly studied biomarker are the serum alphafetoprotein levels[1-11]. However, other biomarkers have recently been reported to be associated with the prognosis of HCC patients undergoing to LT. This review summarizes clinical data on these new biomarkers.

BIOMARKERS

Malondialdehyde

Oxidative stress can lead to membrane lipid peroxidation, which creates many end products, including malondialdehyde, which is a low molecular weight aldehyde that is produced during the degradation of cellular membrane phospholipids. It is formed when free radicals attack polyunsaturated fatty acids. Malondialdehyde can be released into the extracellular space, and it can ultimately reach the bloodstream. Therefore, it has been used as a circulating biomarker of lipid oxidation[12,13].

Some studies have reported higher levels of serum malondialdehyde in HCC patients[14-16] and patients with chronic liver disease than in healthy controls[17,18]. Additionally, studies have reported that the tumoral tissue of HCC patients has higher malondialdehyde concentrations than non-tumoral tissue[19]. Studies have also found higher free radical intensity in the erythrocytes of HCC patients than in healthy controls[20], higher serum concentrations of reactive oxygen metabolites in HCC patients who exhibit recurrence after curative treatment by radiofrequency ablation or surgical resection[21], and higher circulating lipid peroxide levels prior to LT in patients who do not survive LT than in survivors[22].

A study by our team reported, for the first time, that serum malondialdehyde levels prior to LT were higher in non-surviving patients than in patients who survived for one year after LT. We also found an association between serum malondialdehyde levels in HCC patients prior to LT and their survival at one year after LT[23]. These findings are consistent with those from other studies that have reported an association between circulating malondialdehyde levels and mortality in patients with sepsis[24], traumatic brain injuries[25], brain infarctions[26] and spontaneous intracerebral hemorrhaging[27].

Total antioxidant capacity

The production of reactive oxygen species (ROS) is balanced by the production of antioxidant defenses, and the analysis of total antioxidant capacity (TAC) could provide a global information in respect to the antioxidant status[28].

Some studies have found lower circulating TAC levels in LT patients than in healthy controls[18], and lower circulating TAC levels in HCC patients than in healthy controls[14,15].

A study by our team was the first to find that serum TAC levels prior to LT were lower in non-surviving than in surviving patients during the first one year after LT[29]. Besides, we found that there is an association between low serum TAC levels in HCC patients prior to LT and their survival at one year after LT. In addition, we found a negative association between serum levels of TAC and malondialdehyde; thus, patients with lower serum TAC levels showed higher lipid peroxidation.

I think that those findings could suggest that it is possible that non-survivor LT patients remains during the first one year after LT with low serum TAC levels and high serum malondialdehyde levels (due to a higher lipid peroxidation because the high ROS production is not balanced by an insufficient antioxidant capacity) compared to survivor patients.

Antioxidant agents have been shown to reduce malondialdehyde concentrations in animal models of sepsis[30] and brain trauma[31] as well as in clinical trials involving septic newborns[32], acute ischemic stroke[33] and traumatic brain injuries[34]. Additionally, in a clinical trial of traumatic brain injuries[34], the administration of antioxidant agents reduced mortality rate. Thus, since non-surviving HCC patients showed higher serum malondialdehyde levels prior to LT than surviving patients, it could be interesting to explore the benefit of the administration of antioxidant agents to HCC patients undergoing LT. Antioxidant treatment could potentially improve their prognoses, especially for patients with a higher oxidative state.

Caspase-cleaved cytokeratin-18

Apoptosis, which leads to active and programmed cell

elimination, is increased in liver diseases[35-37]. Two main pathways exist (extrinsic and intrinsic) for cell death by apoptosis. The apoptotic extrinsic pathway is initiated when the tumor necrosis factor receptor superfamily (TNFRSF) is activated by its ligand (TNFSF). This leads to the formation of a death signal that activates caspase-8 and ultimately activates caspase-3. The intrinsic apoptotic pathway is activated *via* oxygen free radicals, interleukin (IL)-1, IL-6 and nitric oxide. These factors release cytochromes from the mitochondria to the cytosol, which activates caspase-3. Thus, both apoptotic pathways ultimately activate caspase 3, which leads to cell death.

Cytokeratin-18 is the main protein found in the intermediate filaments of the liver and is present in most parenchymal and epithelial cells. During hepatocyte apoptosis, cytokeratin-18 is cleaved by caspases and can be released into the bloodstream as caspase-cleaved cytokeratin (CCCK)-18[35-39], which can be detected using M30 monoclonal antibodies[40,41].

Some studies have reported higher circulating CCCK-18 levels in patients with tumoral diseases than in healthy controls[42,43] and in patients with tumoral diseases that had a poor evolution[44-48]. Additionally, HCC patients have higher circulating CCCK-18 levels than healthy controls[49,50] or cirrhotic patients[51,52]. Studies have reported an association between serum CCCK-18 levels and mortality in HCC patients[53].

A study by our team found, for the first time, that serum CCCK-18 levels prior to LT were higher in non-surviving patients than in patients who survived for one year after LT. Additionally, an association was found between serum CCCK-18 levels in HCC patients prior to LT and their survival for one year after LT[54]. These findings are consistent with the results of other studies that have shown that circulating CCCK-18 levels are associated with the prognosis of patients with various tumoral diseases[44-48], HCC[53], sepsis[55], traumatic brain injury[56] and cerebral artery infarction[57]. Additionally, circulating CCCK-18 levels have been associated with metastasis[45], serum AFP levels[46,54] and tumor size[47,48].

Soluble CD40 ligand

Soluble CD40 ligand (sCD40L) is a member in the TNFSF of proteins. It has proinflammatory and prothrombotic effects when bound to its receptor, CD40, which is also a member of the TNFRSF[58-65]. CD40L is mainly found in platelets and activated T-lymphocytes, although it is also present in smooth muscle cells, endothelial cells, microglia, monocytes, and B cells. When CD40L is cleaved, it is released into circulation and is present in its soluble form, sCD40L[58-65].

Some studies have reported higher circulating sCD40L levels in patients with ischemic stroke[66-69], acute coronary syndrome[70,71], and sepsis[72,73] than in healthy subjects. Additionally, high circulating sCD40L levels are associated with a poor prognosis in patients with ischemic stroke[69], acute coronary syndrome[74], sepsis[72,73] and traumatic brain injuries[75]. Patients with chronic hepatitis C virus infection[76], cirrhosis[77], and non-alcoholic fatty liver disease have been shown to exhibit higher circulating sCD40L levels than control subjects[78]. Furthermore, high circulating sCD40L levels are associated with a poor prognosis in HCC patients[79].

A study by our team was the first to report that serum sCD40L levels prior to LT were higher in patients who did not survive for one year after transplantation than in the surviving patients, and an association was also found between serum sCD4L levels in HCC patients prior to LT and survival for one year after LT[80]. These findings are consistent with the results of other studies reporting an association between circulating sCD40L levels and mortality in patients with cerebral infarction[69], acute coronary syndrome[74], sepsis[72,73] and traumatic brain injuries[75].

Circulating sCD40L levels could play a role in patients receiving LT for HCC by their proinflammatory[81,82] and procoagulant[83-88] effects. The proinflammatory effects of sCD40L may be due to an increase in the expression of proinflammatory mediators such as IL-1, IL-6, IL-12, TNF-alpha and interferon-gamma[81,82]. The procoagulant effects of sCD40L may be due to the induction of tissue factor expression[83-86], reduced expression of thrombomodulin[85,86] and its binding to glycoprotein Ⅱb/Ⅲa platelet receptor[87,88]. These proinflammatory and procoagulant effects could potentially favor the development of vascular thrombosis and organ dysfunction, ultimately resulting in patient death.

The statin administration has been associated with a reduction of circulating sCD40L levels in patients with coronary artery disease[89-91] and an improvement in the prognosis of patients with ischemic stroke[92] and infections[93-96]. Therefore, as non-surviving HCC patients showed higher serum sCD40L levels prior to LT than patients who survived for one year after LT, it could be interesting to explore the benefit of administering sCD40L modulators to HCC patients who are undergoing to LT to improve their prognosis, especially for patients with higher sCD40L levels.

Substance P

Substance P is a member of the tachykinin family, which is distributed by the central and peripheral nervous, respiratory and urinary systems and by the gut. Tachykinins may play a role in nociceptive responses, inflammation, vasodilation and plasma protein extravasation[97-99].

Circulating substance P levels are elevated in patients with liver diseases compared to control subjects[100-106] and in patients with severe liver diseases[104-106].

A study by our team was the first to report that serum levels of substance P prior to LT were higher in patients who did not survive for one year after LT than in surviving patients. The study also found an association between serum levels of substance P in HCC patients prior to LT and mortality within one year after LT[107].

These findings are consistent with the results of other studies that have reported an association between circulating serum P levels and mortality in patients with traumatic brain injuries[108] or ischemic stroke[109].

Substance P plays a role in the inflammatory response by producing inflammatory cytokines such as IL-1, IL-6 and TNF-alpha[110-114]. Various agents that reduce substance P activity have been identified in animal models of ischemic stroke[115-117] and traumatic brain injury[118,119]. These agents have been associated with a reduction in the inflammation process and edema. HCC patients who did not survive for one year after LT showed higher serum substance P levels prior to LT than surviving patients. Therefore, it could be interesting to explore the benefit of administering agents to control substance P activity to HCC patients undergoing LT, especially in patients with high circulating substance P levels.

Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio

The blood neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have both been used as biomarkers to evaluate systemic inflammatory responses. A meta-analysis published in 2017 by Zheng *et al*[120] analyzed the association between the NLR and PLR in the blood of HCC patients prior to receiving different treatments and its overall survival and HCC recurrence. The treatments included curative resection, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), LT and chemotherapy. The authors examined the associations between the NLR and all treatments combined and individually. They found an association between a high NLR and both of the outcomes (poor overall survival and HCC recurrence) for all types of treatment. They also reported an association between a high NLR and survival when specifically analyzing LT. However, no association was found between the NLR and HCC recurrence when specifically analyzing LT. The authors also found an association between a high PLR and poor outcomes for all treatments combined and when analyzing LT specifically.

C-reactive protein

C-reactive protein (CRP) is synthesized in the liver by hepatocytes in response to factors released by macrophages and adipocytes during inflammation and afterwards is released to blood; thus, blood levels of CRP increase in response to inflammation. Elevated blood CRP levels are associated in multivariate analyses with an increase in the risk of HCC recurrence and decreased survival in patients undergoing LT for HCC[121,122], overall in patients with HCC beyond the Milan criteria[121].

Des-gamma-carboxy prothrombin or protein induced by vitamin K absence or antagonist Ⅱ (PIVKA-Ⅱ)

Des-gamma-carboxy prothrombin (DCP) is a nonfunctional prothrombin form produced by the liver. The normal liver converts the glutamic acid residues in the N-terminal portion of prothrombin by carboxylation in gamma-carboxyglutamic acid residues before its release into the peripheral blood. In many of HCC cells, the vitamin K dependent carboxylase that produces this carboxylation is absent; thus, an abnormal prothrombin is secreted. Several studies have found in multivariate analyses that high blood DCP levels are associated with a higher risk of HCC recurrence in HCC patients who undergo LT[123-127].

Glypican-3

Glypican (GPC)-3 is a member of the glypican protein family, which plays a role in regulating cell division and growth. One study reported that the protein expression of GPC-3 in HCC tissue samples prior to LT was associated with a higher rate of HCC recurrence after LT[128]; in addition, there was found that GPC-3 was expressed in 68% of HCC tissues, but not in adjacent non-tumoral tissues and in tissues of liver controls. Another study found that serum GPC-3 levels were higher in HCC patients than in cirrhosis patients[129]; however, the study did not examine the prognostic role of serum GPC-3 in HCC patients prior to LT.

Human telomerase reverse transcriptase messenger ribonucleic acid

Human telomerase reverse transcriptase messenger ribonucleic acid (h-TERT mRNA) is a ribonucleoprotein polymerase that maintains telomere ends in chromosomes. High h-TERT mRNA expression in the peripheral blood of HCC patients who undergo LT has been associated with decreased survival and increased HCC recurrence[130,131]; however, in another study, h-TERT mRNA concentrations in the peripheral blood were not associated with HCC recurrence after LT[132]. Therefore, additional research is necessary to determine the prognostic role of h-TERT mRNA expression in the peripheral blood of HCC patients prior to LT.

Matrix metalloproteinase-9

Matrix metalloproteinase (MMP)-9 is a member of the matrix metalloproteinases (MMPs), which are involved in degradation and remodeling of the extracellular matrix. MMPs play a role in physiological functions such as morphogenesis, tissue remodeling and the menstrual cycle. They are also involved in various diseases such as arthritis, tumors, atherosclerosis and sepsis. The activity of MMPs is regulated by several tissue inhibitor of matrix metalloproteinases (TIMPs).

Contradictory results have been found with regard to MMP-9. Patients who undergo LT for HCC and have high MMP-9 expression in the tumor have exhibited an unfavorable rates of overall survival and HCC recurrence[133,134]. Another study in patients undergoing LT due to HCC or for cirrhosis without HCC found that high serum MMP-9 levels at one week after LT were associated

with a higher rate of LT rejection[135]. However, one study also reported that high serum MMP-9 levels and low serum TIMP-1 levels in HCC patients receiving different treatments (curative resection, TACE, thermoablation, and LT) were associated with a higher survival rate, although the study did not specifically examine patients receiving LT because the sample size for that group was small[136]. Our group has previously reported a lower survival rate in patients with cerebral artery infarction[137], traumatic brain injury[138] and sepsis[139,140] who have high serum TIMP-1 levels than in patients who have low TIMP-1 levels. Therefore, additional research is necessary to establish the prognostic role of MMP-9 expression in the peripheral blood of HCC patients prior to LT.

E-cadherin

E-cadherin is a member of the cadherin family of proteins, which are cell adhesion molecules that participate in the formation of junctions between cells. One study found that high serum levels of soluble E-cadherin were associated with increased recurrence of HCC after a curative resection[141]. Another study of HCC patients who underwent LT found that E-cadherin expression in the liver was associated with HCC recurrence after LT[142].

Beta-catenin

Beta-catenin is a member of the catenin family of proteins, which also constitute a group of cell adhesion molecules that are involved in the formation of bonds between cells. A study of HCC patients who underwent LT found that beta-catenin expression in the liver was associated with HCC recurrence after LT[142]. However, in other recently published study, no association was found between beta-catenin expression in the liver prior to LT and the survival of HCC patients[143]. Therefore, additional research is necessary to establish the prognostic role of beta-catenin expression in the liver in HCC patients prior to LT.

AFP

AFP is a glycoprotein that is produced by the yolk sac and the fetal liver during fetal development. It is the most abundant plasma protein in the human fetus. Increased values are found in newborns (values gradually decrease to normal over the first year of life), pregnant women (values return to normal after delivery), and patients with various AFP-producing tumors such as HCC and tumors of the ovary and testis.

The blood AFP level is the most extensively studied biomarker in HCC patients undergoing LT. Elevated blood AFP levels are associated with decreased survival[144] as well as an increase in HCC recurrence[145] in patients undergoing LT for HCC.

A review of 13 observational studies published in 2012 involving 12,159 patients who underwent LT for HCC examined the role of pre-LT circulating AFP levels in predicting survival and HCC recurrence[144]. Nine of the 13 studies reported data about pre-LT serum AFP levels and survival. Only four studies reported absolute serum AFP values for all included patients, and the other studies used varying cut-off points for serum AFP levels. This heterogeneity precluded pooling of the data for a valid meta-analysis. The majority of the studies concluded that a high pre-LT serum AFP level was an independent predictor of death following LT for HCC. These studies also suggested that serum AFP levels higher than 1000 ng/mL may predict poorer survival. Ten of the 13 studies reported data on HCC recurrence and pre-LT serum AFP values. All of these studies concluded that high AFP levels were associated with increased HCC recurrence following LT for HCC. The authors were unable to perform a meta-analysis on this research question due to the heterogeneity in the data reported by the studies. Additionally, some of the studies included in the review found that pre-LT serum AFP levels were correlated with vascular invasion and poor differentiation of HCC.

A review and meta-analysis published in 2016 examined the prognostic role of biomarkers in HCC recurrence in patients who underwent LT for HCC[145]. The review included 49 studies with a total of 13693 patients that reported data on pre-LT serum AFP levels and HCC recurrence. However, the studies had 88% heterogeneity due to their use of varying definitions and cut-off values for AFP. Therefore, it was not possible to conduct a valid meta-analysis for this topic. However, a meta-analysis was performed using 17 of the studies with different cut-off values for pre-LT serum AFP levels, but the meta-analysis required a cut-off value higher than 400 ng/mL. In this analysis, an association was found between elevated pre-LT serum AFP levels and the risk of HCC recurrence (HR = 2.69; 95%CI: 2.08-3.47), with a heterogeneity of 46%.

Dickkopf-1

In several studies have been found higher circulating Dickkopf-1 (DKK1) levels in HCC patients than in healthy subjects[146-149] or than in patients with liver cirrosis without HCC[150,151]. In addition, in a meta-analysis published in 2014 including 4 studies[152] and in other recently published study[153] was found that higher DKK1 expression levels in HCC patients were associated with lower survival. Besides, in one study was found that higher DKK1 expression is associated with lower survival and higher recurrence in HCC patients after LT[154].

Vascular endothelial growth factor

In a meta-analysis of 11 studies was found that high serum Vascular endothelial growth factor (VEGF) leves in HCC patients were associated with lower survival[155]. In addition, in one study was found that high plasma VEGF levels in HCC patients previously to LT were associated with HCC recurrence and survival[156].

Caspase-1

Pyroptosis is a form of programmed cell death, which is dependent of caspase-1. In some studies has been

Table 1 New prognostic biomarkers in patients undergoing liver transplantation for hepatocellular carcinoma

Biomarker	Alteration	Outcome	Ref.
Malondialdehyde	High circulating levels	Lower survival	[23]
Total antioxidant capacity	High circulating levels	Lower survival	[29]
Caspase-cleaved cytokeratin-18	High circulating levels	Lower survival	[54]
Soluble CD40 ligand	High circulating levels	Lower survival	[80]
Substance P	High circulating levels	Lower survival	[107]
Neutrophil to lymphocyte ratio	High circulating ratio	Lower survival	[120]
Platelet to lymphocyte ratio	High circulating ratio	Lower survival	[120]
C-reactive protein	High circulating levels	Lower survival	[121,122]
Des-gamma-carboxy prothrombin	High circulating levels	Higher recurrence	[123-127]
Glypican-3	High HCC expression	Higher recurrence	[128]
H-TERT mRNA	High peripheral blood expression	Lower survival	[130,131]
E-cadherin	High HCC expression	Higher recurrence	[142]
Beta-catenin	High HCC expression	Higher recurrence	[142]
Dickkopf-1	High HCC expression	Lower survival	[154]
Vascular endothelial growth factor	High circulating levels	Lower survival	[156]

HCC: Hepatocellular carcinoma; H-TERT mRNA: Human telomerase reverse transcriptase messenger ribonucleic acid.

found lower caspase-1 expression in HCC tissues[157,158]. In a study was determined caspase-1 expression in HCC patients (from HCC tissues and adjacent normal tissues) and in hepatocyte cell lines[157]. There was found a significant decrease in caspase-1 expression in HCC tissues compared to adjacent normal tissues and hepatocyte cell lines. Besides, the use of berberine increased the expression of caspase-1, decreased cell number, and increased cell swelling in hepatocyte cell lines; and the use of the caspase-1 inhibitor Ac-YVAD-CMK attenuated the effects of berberine.

However, in one study has been found that liver tissue of patients infected with hepatitis C virus (HCV) showed caspase-1-mediated pyroptosis[159]. Besides, in other study of patients with resection of HCC was found lower survival in patients with high of caspase-1 expression in normal tissues[160].

Angiopoietin-2

Angiopoietin-2 is a protein that is involved in angiogenesis and inflammation[161]. In a recently published study of chronic HCV patients treated with direct acting antivirals (DAA) was found that angiopoietin-2 in liver tissue was related with the risk of HCC recurrence or de novo ocurrence.

Another interesting finding of that study was that patients with HCC recurrence or de novo ocurrence had significantly higher portal pressure than patients never developing HCC[162]; and in previous studies was found that portal hypertension was associated with poor prognosis in patients undergoing to LT[163] or with HCC[164,165].

The risk of HCC occurrence or recurrence following DAA remains unclear due to that the results of different studies are contradictories. In a review published in 2017 including 10 studies was found in meta-analyses a higher incidence of HCC occurrence and HCC recurrence with the administration of DAA[166]. However, in meta-regression analyses after adjusting for study follow-up and age, DAA therapy was not associated with higher HCC de novo ocurrence and neither with HCC recurrence. In the study by Faillaci *et al*[162] was found that the use of DAA was associated with de novo HCC, and that this risk is higher in patients with higher angiopoietin-2 expression.

Genomic

The Cancer Genome Atlas (TCGA) Research Network published in 2017 the genomic characterization of HCC[167]. There were analyzed 363 HCC cases by whole-genome sequencing and DNA copy number, and 196 HCC cases by DNA methylation, mRNA, miRNA, and proteomic expression. In total, 12136 genes had non-silent mutations, and 26 genes were determined to be significantly mutated genes. Of these 26 genes, 18 were reported in at least one previous HCC genome sequencing study and 8 were not previously associated with HCC. Whithin of know mutated genes, the most included TERTpromoter (51%), TP53 (31%), CTNNB1 (27%), ALB (13%), APOB (10%), ARID1A (7%), AXIN1 (8%), ARID2 (5%), BAP1(5%), KEAP1 (5%), RB1 (4%), and NFE2L2 (3%). There were identified 8 novel mutated gene with a low frequence (2%-3% of HCC patients), including LTZR1, EEF1A1, AZIN1, RP1L 1, GPATCH4, CREB3L3, AHCTF1, and HIST1H1C. In addition, other two mutated genes previously associated with other cancer types were associated with HCC in this study, F3B1 and SMARCA4. Besides, integrative clustering of datasets of DNA copy number, DNA methylation, mRNA expression and miRNA expression could define three HCC subtypes (iClust 1 to 3), and iClust1 subtype had a poor prognosis. In addition, the analysis of these mutations and pathways provide potential directions for future potential therapeutic in HCC patients by the use of inhibitors of WNT, MDM4, MET, VEGFA, MCL1, IDH1, TERT. Thus, this genome-wide characterization has been very important in improving our knowledge about mutated genes associated with HCC, prognostic gene signatures and potential treatments[168].

CONCLUSION

Various macromorphological factors measured prior to LT have been classically used to estimate the outcomes of HCC patients undergoing LT. Additionally, the determination of some valid biomarkers prior to LT could help predict the prognoses of HCC patients undergoing LT. The most frequently examined biomarker is the serum AFP level. Recently, an association was reported between decreased survival rates and high blood levels of malondialdehyde, TAC, CCCK-18, sCD40L, substance P, CRP, and VEGF, NLR and PLR in blood, high peripheral blood expression of h-TERT mRNA, and high HCC expression of DKK1. In addition, an association has been found between increased HCC recurrence and high blood levels of Des-gamma-carboxy prothrombin, and high HCC expression of GPC-3, E-cadherin and beta-catenin. Additional research is necessary to establish the prognostic role of these biomarkers for HCC prior to LT. Furthermore, some of these biomarkers are also interesting because their potential modulation could help to create new research lines for improving the outcomes of those patients. Those new biomarkers are summarized on Table 1.

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