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EDITORIAL

Sirtuin 1 in regulating the p53/glutathione peroxidase 4/gasdermin D axis in acute liver failure

Swati Katoch, Vikram Patial

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Abstract

In this editorial, we comment on the article by Zhou *et al*. The study reveals the connection between ferroptosis and pyroptosis and the effect of silent information regulator sirtuin 1 (SIRT1) activation in acute liver failure (ALF). ALF is characterized by a sudden and severe liver injury resulting in significant hepatocyte damage, often posing a high risk of mortality. The predominant form of hepatic cell death in ALF involves apoptosis, ferroptosis, autophagy, pyroptosis, and necroptosis. Glutathione peroxidase 4 (GPX4) inhibition sensitizes the cell to ferroptosis and triggers cell death, while Gasdermin D (GSDMD) is a mediator of pyroptosis. The study showed that ferroptosis and pyroptosis in ALF are regulated by blocking the p53/GPX4/GSDMD pathway, bridging the gap between the two processes. The inhibition of p53 elevates the levels of GPX4, reducing the levels of inflammatory and liver injury markers, ferroptotic events, and GSDMD-N protein levels. Reduced p53 expression and increased GPX4 on deletion of GSDMD indicated ferroptosis and pyroptosis interaction. SIRT1 is a NAD-dependent deacetylase, and its activation attenuates liver injury and inflammation, accompanied by reduced ferroptosis and pyroptosis-related proteins in ALF. SIRT1 activation also inhibits the p53/GPX4/GSDMD axis by inducing p53 acetylation, attenuating LPS/D-GalN-induced ALF.

Key Words: Acute liver failure; Ferroptosis; Gasdermin D; Pyroptosis; p53; Silent information regulator sirtuin 1

Core Tip: Ferroptosis and pyroptosis are crucial modes of hepatic cell death in acute liver failure (ALF), and their close association leads to the sudden progression of liver failure. Silent information regulator sirtuin 1 inhibits p53 activity by deacetylation, thereby promoting cell survival. Inhibition of p53 activity affects downstream regulators like Glutathione peroxidase 4 (GPX4) and Gasdermin D (GSDMD). The overexpression of GPX4 and reduced levels of GSDMD protect the cell from pyroptosis and ferroptosis, indicating the close link between these mechanisms in ALF.

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INTRODUCTION

Acute liver failure (ALF), also referred to as fulminant hepatic failure, is a rare yet serious condition characterized by the rapid deterioration of liver function, often occurring within a span of days to weeks. It can be caused by various factors, including drug overdose, viral infections, and autoimmune diseases[1]. This rapid deterioration of liver function can lead to severe complications, including hepatic encephalopathy, coagulopathy (bleeding disorders), and multi-organ failure [2]. According to a report, patients with ALF had 40.02% mortality[3]. ALF accounts for 6% of all liver disease-related deaths in the United States, and 3000 cases are reported annually. It is more common in Americans than other racial groups and more common in women than men. The peak incidence of ALF is at a relatively young age of 35 years in women and 45 years in men[4]. Drug-induced liver injury is the most common cause of ALF in developed countries, accounting for over 50% of cases. It can be caused by various medications, including acetaminophen (paracetamol) overdose, certain antibiotics, anti-epileptic drugs, and herbal remedies[5]. Recent studies have proposed several cell death pathways, including ferroptosis, pyroptosis, necroptosis, and apoptosis, that are important in the development of ALF[6, 7]. Among them, the two distinguishing programmed cell death processes that are distinct from autophagy, apoptosis, and necrosis are ferroptosis and pyroptosis. Both of these processes are vital for the development of ALF as they each modulate distinct inflammatory and immunological responses[8].

The main mechanism behind ferroptosis is reactive oxygen species (ROS)-dependent regulated cell death, with lipid peroxidation, intracellular iron overload, and decreased glutathione peroxidase 4 (GPX4) activity serving as key indicators. The Fenton process results in the production of ROS, which changes hydrogen peroxide into hydroxyl radicals and subsequently causes lipid peroxidation[9]. ROS growth is regulated by the inhibitory activity of GPX4, an enzyme that uses hydrogen ions to neutralize lipid peroxides and hydrogen peroxide. Reduced glutathione (GSH) is transformed into glutathione disulfide (GSSG) by GPX4[10]. In addition to GPX4's basic function of preserving ROS levels, numerous other pathways are necessary to sustain GPX's antioxidant activity. System Xc- is a heterodimeric antiport system comprising the subunits SLC3A2 and SLC7A11 that import cystine and output glutamate. The imported cystine is converted into cysteine and GSH to maintain redox equilibrium and shield the cells from ferroptosis[11]. The primary mechanism that sustains the effectiveness of GPX antioxidant action is System Xc-, which inhibits a sequence of processes that lead to a decrease in GSH levels, lipid peroxidation, and, ultimately, ferroptosis[12].

Due to p53's transcriptional inhibition of SLC7A11, cells are more susceptible to ferroptosis and absorb cystine less efficiently. The cellular response to various triggers of stress, such as hypoxia, starvation, DNA damage, and oncogene activation, is greatly influenced by p53. Furthermore, by inhibiting cystine metabolism and ROS activity, p53 promotes ferroptosis[13].

Pyroptosis is an acute inflammatory form of programmed cell death that is mostly provoked by either canonical or noncanonical inflammasomes. It is characterized by the morphological enlargement of cells followed by lysis, ultimately releasing intracellular material[14]. The liver is constantly exposed to various gut-derived microbial particles known as pathogen-associated molecular patterns (PAMPs) due to the tight connection between portal circulation and the intestines. PAMPs excite local immune cells[15]. When risk signals are detected, intracellular multiprotein complexes known as canonical inflammasomes are formed. These inflammasomes activate caspase-1, which leads to the maturation of interleukin-1 beta (IL-1β), IL-18, and IL-37, ultimately causing pyroptosis. Caspase-11 is activated by noncanonical inflammasomes, causing pyroptosis[16]. Gasdermin D (GSDMD) is a pore-forming protein that incites pro-inflammatory cytokine release and causes pyroptosis[17]. PAMPs stimulate distinct inflammasomes to initiate caspase-1, which subsequently cleaves GSDMD, the pyroptosis executor, into its active N terminal and inactive C terminal. The C-terminal regulatory domain (GSDMD-C) and the pyroptotic N-terminal domain (GSDMD-N) of GSDMD are joined by a linker domain. Inflammatory caspases (caspase-1, caspase-4, and caspase-5) break the linker domain of GSDMD, releasing GSDMD-N from its autoinhibitory GSDMD-C. GSDMD-N demonstrates a remarkable resemblance to membrane lipids, where it oligomerizes to produce pores with a diameter of around 20 nm, causing swelling and cell lysis, while GSDMD-C stays in the cytoplasm[18].

Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase, is believed to protect cells from oxidative stress injury by mediating Nrf2 production and its downstream targets[19]. SIRT1 plays a complex function in stress responses, energy metabolism, inflammation, and redox balance through the acetylation and deacetylation of certain transcription factors and proteins, including p53[20]. Zhou *et al*[21] discussed the method by

which SIRT1 reduces ALF and how it is linked to hepatocyte death that occurs widely and involves ferroptosis and pyroptosis[21].

ROLE OF p53/GPX4/GSDMD AXIS IN ACUTE LIVER FAILURE

Zhou *et al*[21] have carefully examined the process by which p53/GPX4/GSDMD signaling pathway blockade caused by SIRT1 activation decreases ferroptosis and pyroptosis in ALF (Figure 1). The increased activity of the enzyme biomarkers alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in human ALF is linked to elevated levels of inflammatory factors, such as tumor necrosis factor-α (TNFα), IL-1β, and IL-6. Furthermore, ferroptosis-related antioxidant protein levels of GPX4 and SLC7A11 drop in ALF, worsening iron deposition and leading to increased expression of GSDMD[21]. It is unclear how ferroptosis and pyroptosis are related to fulminant hepatitis in humans, despite the fact that the etiology of LPS/D-GalN-induced ALF in mice is quite similar to that in humans.

GSDMD and GPX4 are essential for ferroptosis and pyroptosis to occur. Conditions leading to GPX4 instability or suppression make cells more susceptible to ferroptosis or even lead to ferroptotic cell death, whereas sufficient GPX4 activity and GSH synthesis are necessary to prevent ferroptosis[22]. A recent study in a murine model found that ferroptosis was significantly involved in liver failure produced by acetaminophen. The results showed higher levels of TNFα, interleukins, and PTGS2, a well-known marker for ferroptosis. This process was considerably suppressed by ferrostatin-1, an inhibitor that is unique to ferroptosis. Ferroptosis may be a viable therapeutic target for liver failure, according to these findings[23]. Increased ROS levels, decreased System Xc-activity, and suppressed GPX4 levels are the main inducers of ferroptosis[24]. The LPS/D-GalN-induced liver failure model was reported to have decreased levels of SLC7A11, HO-1, and GPX4, along with increased ROS production, indicating System Xc- involvement in ferroptosis[25]. The inflammatory action is further prolonged by GSDMD-mediated hepatocyte pyroptosis, which stimulates macrophages by escalating the levels of monocyte chemotactic protein 1/CC chemokine receptor-2[18]. A study reported that pre-administration of oyster-derived Tyr-Ala (YA) peptide improves the elevated levels of GSDMD, along with its regulatory factors like caspase-1, IL-1β and TNFα in the LPS/D-GalN induced ALF model[26]. Many researchers reported that GSDMD gene knockout ameliorates pyroptosis and ferroptosis with reduced inflammatory reactions and hepatocyte loss, which improves ALF[27,28].

The non-classical process of pyroptotic cell death is mediated by caspase-11, which is implicated in myeloid cell knockout[29]. This process was seen in mice lacking the GPX4 gene that were susceptible to a deadly infection and had septic myeloid cells. GPX4 suppressed the caspase-1-dependent NLRP3 inflammasome, suggesting a comprehensive role of GPX4 against pyroptosis[30]. According to a different study, 3,4-dihydroxyphenylethyl alcohol glycoside (DAG) prevents hepatocyte ferroptosis and pyroptosis, which lowers ALF in mice caused by acetaminophen. DAG further decreased the levels of proinflammatory cytokines, histological changes, hepatic neutrophil infiltration, and serum ALT and AST. It also suppressed the levels of MDA adducts and the depletion of GSH, CAT, and SOD enzymes. *In vitro*, in mouse AML12 hepatocytes exposed to acetaminophen, DAG demonstrated a dose-dependent suppression of proinflammatory factors (IL-1β and IL18), ROS, and the reduction of GSH depletion. Interestingly, in liver tissues and AML12 hepatocytes, DAG increased the expression of GPX4 and decreased that of HO-1, NLRP3, caspase-1, and GSDMD[31].

The p53 tumor suppressor protein is a critical cell cycle and apoptosis regulator. p53 regulates the progression of liver injury and regeneration after acetaminophen overdose[32]. p53 knockout mice (p53KO) showed prolonged steatosis, lower mitochondrial DNA content, and reduced expression of mitochondrial transcription factor A and mitochondrial complexes in acetaminophen-induced liver injury. It also altered metabolic homeostasis and activated proinflammatory and proliferative signaling. Prolonged steatosis in the p53KO group was also linked with p53 targets related to fatty acid balance, SREBP2 protein, and GAMT mRNA expression[32]. Zhou *et al*'s study[21] demonstrated that the inhibition of p53 and increased GPX4 in the ALF mouse model reduced the inflammatory responses, AST and ALT levels, and ferroptotic events (depletion of GPX4, GSH, and SLC7A11, as well as iron buildup). A cross-talk between ferroptosis and pyroptosis was observed, as evidenced by the reduction of p53 expression and the elevation of GPX4 following GSDMD knockout. Furthermore, ALT and AST levels, ferroptosis markers, and GSDMD were markedly enhanced in response to GPX4 knockdown[21]. The findings suggest the possibility of a positive feedback loop and the alleviation of ferroptosis and pyroptosis in ALF caused by disrupting the p53/GPX4/GSDMD signaling pathway. Another study showed that altering GPX4 protein expression did not influence p53 levels; however, it did operate indirectly by controlling GSDMD, indicating that GPX4 is a downstream regulator of p53. p53-driven ferroptosis is produced in a GPX4-independent manner, and p53 levels remain unaffected by the deletion of ACSL4 and GPX4. However, p53 transcription decreases with GPX4 augmentation, indicating the correlation between GPX4, GSDMD, and p53 in ferroptosis and pyroptosis[33].

SIRT1, a NAD-dependent deacetylase, mediates the function of p53 by direct deacetylation. According to one study, negative regulation of SIRT1 exacerbated the acute hepatic proinflammatory response and induced pyroptosis[34]. However, SIRT1 overexpression eliminated p53 acetylation levels and decreased the release of hepatic enzymes, hepatic oxidative stress, and inflammation in acetaminophen-induced liver injury[35]. The immediate target gene of p53 is microRNA-34a (miR-34a), which concurrently activates p53 *via* SIRT1. The miR-34a/SIRT1/p53 signaling pathway, crucial for cell division and death, creates a positive feedback loop in which p53 stimulates miR-34a, and miR-34a promotes p53 by blocking SIRT1. Human patients or animal models with several liver disorders, including liver fibrosis, have been reported with higher expression levels of miR-34a[36]. SIRT1 overexpression attenuates liver fibrosis by decreasing p53 acetylation and caspase activation in apoptosis[37]. In the case of myocardial ischemia-reperfusion injury, SIRT1 activation was found to reduce ferroptosis-induced cardiac cell death by overexpression of SLC7A11 and inhibition of p53, indicating the close link of the SIRT1/p53/SLC7A11 axis[38]. Mice treated with resveratrol, a small-molecule

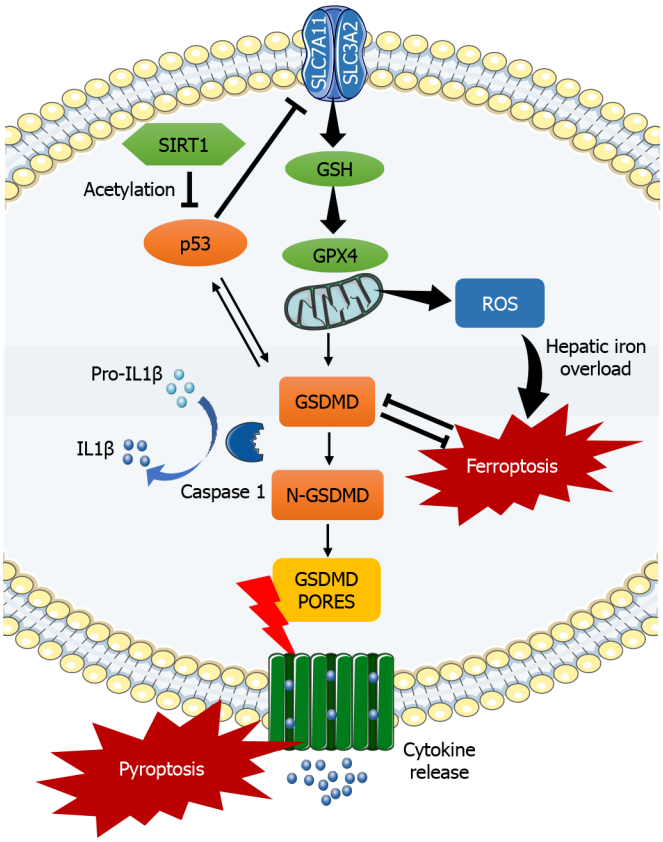

Figure 1 The activation of sirtuin 1 suppresses ferroptosis and pyroptosis in acute liver failure by inhibiting p53, glutathione peroxidase 4, and gasdermin D. The silent information regulator sirtuin 1 blocks p53 deacetylation and inhibits the glutathione peroxidase 4 (GPX4)/gasdermin D (GSDMD) signaling pathway, which in turn reduces hepatic iron overload and the inflammatory response. Ferroptosis and pyroptosis in acute liver failure are reduced by blocking the p53/GPX4/GSDMD signaling pathway. SIRT1: Silent information regulator sirtuin 1; SLC7A11: Solute carrier family 7a member 11; SLC3A2: Solute carrier family 3a member 2; GSH: Glutathione; GPX4: Glutathione peroxidase 4; GSDMD: Gasdermin D; IL1β: Interleukin-1 beta; ROS: Reactive oxygen species.

SIRT1 activator, did not suffer hepatic ischemia-reperfusion injury[39]. Overall, all the findings establish a cross-talk between ferroptosis and pyroptosis with their primary upstream and downstream regulatory mechanisms. The activation of SIRT1 inhibits p53 and GSDMD activity while stimulating GPX4 action, overall blocking the p53/GPX4/GSDMD axis and protecting the cell from ferroptosis and pyroptosis.

CLINICAL IMPLICATIONS OF ACUTE LIVER FAILURE

ALF can have significant clinical implications, ranging from mild symptoms to life-threatening complications. Some common implications related to ALF are hepatic dysfunction, coagulopathy, multi-organ dysfunction, hepatic encephalopathy, infection susceptibility, and various long-term complications[2]. Early recognition, prompt diagnosis, and appropriate management are essential to improve outcomes and reduce morbidity and mortality associated with ALF[3]. Certain naturally occurring substances, such as resveratrol in red wine, have been recognized as SIRT1 agonists. Resveratrol has drawn interest because of its potential health benefits and capacity to activate SIRT1 and replicate the effects of caloric restriction, which have been linked to longer lifespans in various organisms[39]. Synthetic SIRT1 agonist development has also been the focus of researchers for possible medicinal uses. Compared to natural substances, these synthesized molecules may provide a more robust and tailored activation of SIRT1. Researchers are looking at the potential of SIRT1 agonists in cancer, neurological diseases, and metabolic disorders, among other areas. The clinical advantages and safety of SIRT1 agonists in humans are still being assessed through ongoing research and clinical trials, even though SIRT1 activation shows promising results in preclinical studies. It is important to remember that SIRT1 is a multifaceted molecule whose function in human health is currently being studied. This work demonstrated a connection between the upstream regulatory processes and ferroptosis and pyroptosis. More investigations are required to ascertain the possible therapeutic advantages of targeting SIRT1 to treat various metabolic disorders.

CONCLUSION

To sum up, this editorial examines the data supporting the notion that ferroptosis and pyroptosis are essential hepatocyte

death mechanisms in ALF, and that the interplay between these cell death mechanisms promotes the development of ALF. The findings suggest that SIRT1 and p53 can regulate each other in a feedback loop. While SIRT1 has been shown to deacetylate and inhibit p53 activity, thereby promoting cell survival and inhibiting apoptosis, p53 activation can lead to increased expression of SIRT1, which may have various downstream effects on cellular processes. Considering the reported shreds of evidence, we can attenuate ALF by blocking the p53/GPX4/GSDMD signaling pathway and activating SIRT1, which results in reduced ferroptosis and pyroptosis. This signaling pathway, especially SIRT1, might be a promising therapeutic target for liver failure.

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EDITORIAL

Overview of ferroptosis and pyroptosis in acute liver failure

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Abstract

In this editorial, we comment on the article by Zhou *et al* published in a recent issue. We specifically focus on the crucial roles of ferroptosis and pyroptosis in acute liver failure (ALF), a disease with high mortality rates. Ferroptosis is the result of increased intracellular reactive oxygen species due to iron accumulation, glutathione (GSH) depletion, and decreased GSH peroxidase 4 activity, while pyroptosis is a procedural cell death mediated by gasdermin D which initiates a sustained inflammatory process. In this review, we describe the characteristics of ferroptosis and pyroptosis, and discuss the involvement of the two cell death modes in the onset and development of ALF. Furthermore, we summarize several interfering methods from the perspective of ferroptosis and pyroptosis for the alleviation of ALF. These observations might provide new targets and a theoretical basis for the treatment of ALF, which are also crucial for improving the prognosis of patients with ALF.

Key Words: Acute liver failure; Ferroptosis; Pyroptosis; Glutathione peroxidase 4; Gasdermin D

Core Tip: In this review we describe the characteristics of ferroptosis and pyroptosis, and discuss the involvement of the two cell death modes in the onset and development of acute liver failure (ALF). Furthermore, we summarize several interfering methods from the perspective of ferroptosis and pyroptosis for the alleviation of ALF. These observations might provide new targets and a theoretical basis for the treatment of ALF, which is also crucial for improving the prognosis of patients with ALF.

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INTRODUCTION

Acute liver failure (ALF) is a severe clinical syndrome characterized by massive hepatocyte necrosis and acute liver damage in a short period of time with a mortality rate as high as 30%[1]. When ALF occurs, liver function declines sharply, which fails to fulfill the organ's basic physiological actions. Clinically, the main manifestations of ALF are jaundice, ascites, and hepatic encephalopathy[2]. The common causes of ALF include pharmacological liver injury, hepatitis virus, ischemia, and autoimmunity, which account for nearly 80% of the ALF cases[3]. For example, acetaminophen overdose triggers the formation of NOD-like receptor protein 3 (NLRP3) inflammasome, resulting in pyroptosis and ultimately leading to ALF[4]. In addition, acute hepatitis B (AHB) virus infection is the main cause of ALF in many countries[5]. A recent study indicated that 6.6% of patients with AHB developed ALF[6].

Previous studies have established that the primary mode of cell death involved in ALF is apoptosis[7]. As a form of cell-autonomous programmed death, apoptosis triggers a series of reactions by activating the caspase family of proteins, leading to intracellular protein degradation and the elimination of damaged or no longer needed cells[8]. Rutherford *et al* [9] demonstrated that apoptosis was markedly activated in ALF, with notable elevations of apoptosis markers such as tumor necrosis factor-alpha, hepatocyte growth factor (HGF), interleukin-6, and receptor interacting protein kinase 3 (RIPK3). Notably, the elevated levels of HGF and RIPK3 could serve as a confirmatory diagnostic marker and a poorer clinical prognosis for patients suffering from ALF, respectively[10].

Studies over the past 10 years have garnered widespread attention related to two emerging modes of cell death, ferroptosis and pyroptosis, in ALF pathogenesis. Ferroptosis is a form of cell death that relies on iron ions (Fe^{2+}), characterized by the peroxidation of polyunsaturated fatty acids on the cell membrane[11]. Fe^{2+} promotes the generation of lipid peroxides, leading to excessive reactive oxygen species (ROS) production, which further disrupts the integrity of the cell membrane and triggers cell death[12,13]. It is worth noting that GSH peroxidase 4 (GPX4) functions as a crucial enzyme in the ferroptosis pathway, which catalyzes the decomposition of lipid peroxides. When GPX4 activity is inhibited, lipid peroxides accumulate in the cell membrane, ultimately culminating in the onset of ferroptosis[14]. Pyroptosis is a form of cell death with inflammatory characteristics, typically manifested by the formation of numerous small vesicular structures known as pyroptotic bodies[15]. Pyroptotic bodies mediate the cleavage of gasdermin D (GSDMD) by caspase proteins to release its N-terminal fragment. The N-terminus of GSDMD is the main effector of pyroptosis, which is released and inserted into the cell membrane to form holes, leading to rupture of the cell membrane and the release of cell contents, ultimately triggering the onset of pyroptosis[16,17]. These released substances can activate immune cells and trigger severe inflammatory responses[18]. Additionally, the released proinflammatory mediators may further initiate a sustained inflammatory process and create a vicious cycle[19]. The intense inflammatory response may aggravate liver tissue damage and promote the further development of ALF.

Ferroptosis and pyroptosis represent two different modes of cell death, with an increasing body of evidence indicating a potential correlation between them. The release of damage-associated molecular patterns (DAMPs) from plasma membrane pores may be a common feature of ferroptosis, pyroptosis, and necroptosis[20]. Furthermore, the released DAMPs triggered by ferroptosis may promote pyroptosis and necroptosis. GPX4 is a key enzyme in ferroptosis and has also been demonstrated to be implicated in the negative modulation of pyroptosis[21]. Interestingly, GPX4 has been observed to induce a range of other forms of cell death, including apoptosis, autophagy, necroptosis, and pyroptosis[22]. This suggests the possibility of a complex interconnection between ferroptosis and other forms of programmed cell death. It has been demonstrated that iron-activated ROS can induce pyroptosis through the Tom20-Bax-caspase-GSDME pathway, and GPX4 can inhibit the activity of caspase-1, thereby preventing the process of pyroptosis[23]. Additionally, GPX4 functions as a regulator of NOD-, LRR-, and NLRP3-mediated pyroptosis in kidney injury[24]. The interaction between pyroptosis and ferroptosis in epilepsy may be associated with toll-like receptor 4 (TLR4)-mediated neuroinflammation[25]. Ferroptosis has been demonstrated to induce neuroinflammation and the release of a considerable number of inflammatory factors. Among these factors, IL-1β can activate the HMGB1/TLR4 signaling pathway, thereby increasing the production of NLRP3 and IL-1β. This process serves to amplify the inflammatory response by inducing pyroptosis.

In the article by Zhou *et al*[26] entitled 'Silent information regulator sirtuin 1 ameliorates acute liver failure (ALF) *via* the p53/glutathione peroxidase 4/gasdermin D axis', the authors demonstrated that ferroptosis and pyroptosis are key modes of hepatocyte death in the progression of ALF. Therefore, it is crucial to conduct a comprehensive analysis of the regulatory roles of ferroptosis and pyroptosis in ALF. This will not only enhance our understanding of the pathological process of liver failure but also potentially provide theoretical support for the development of new treatment strategies.

MECHANISMS OF FERROPTOSIS AND PYROPTOSIS IN ALF

The mechanisms underlying the occurrence and development of ALF have been described in previous publications[3,10,11,27]. Here, we mainly focus on the roles of ferroptosis and pyroptosis in ALF.

The involvement of ferroptosis in ALF

Ferroptosis has been shown to play important roles in several pathological processes associated with liver diseases[12,14], including ALF[28], which is regulated by lipid peroxidation and iron accumulation[29]. The key process in ferroptosis is the Fenton reaction, in which Fe^{2+} converts lipid peroxides to ROS[30]. As a key regulator of ferroptosis, GPX4 is the only GSH peroxidase isoform capable of regulating lipid peroxidation and ROS levels[31], which could catalyze the decomposition of toxic peroxides depending on the conversion of GSH to oxidized GSH[32]. Additionally, the glutamate/cystine antitransport system (System Xc) is another important regulator of ferroptosis, the inhibition of which would promote the ferroptosis process[33]. It has been indicated that p53 could induce ferroptosis by inhibiting System Xc activity and reducing cystine entry into the cell[34]. Moreover, solute carrier family 7 member 11 (SLC7A11) has been proved to be a crucial upstream regulator of ferroptosis[35], the down-regulation of which inhibits the cysteine metabolic pathway, leading to a reduction in intracellular cystine levels and an indirect inhibition of GPX4 activity[36]. Jiang *et al*[34] found that p53-mediated transcriptional repression of SLC7A11 is critical for ROS-induced ferroptosis. Another study revealed that G3BP stress granule assembly factor 1 (G3BP1) inhibits the entry of p53 protein into the nucleus and reduces SLC7A11 transcription and hepatocyte ferroptosis during ALF[37]. Also, hepatitis B virus X protein exacerbates ALF by promoting iron-mediated cell death through EZH2/H3K27me3-mediated inhibition of SLC7A11[38]. In addition, nuclear factor erythroid 2-related factor 2 (Nrf2) is also an important regulator of ferroptosis[39], and its activation inhibits H_2O_2-induced cellular ferroptosis by modulating the GPX4 pathway[14]. Collectively, these findings suggest that ferroptosis plays a significant role in the development of ALF.

The involvement of pyroptosis in ALF

Pyroptosis, another cell death mode, also triggers significant hepatocyte death in liver failure[40]. In the pathogenesis of ALF, GSDMD can be cleaved by caspase-1 into inflammatory GSDMD-N in the hepatocyte cytoplasm[41]. GSDMD-N recognizes phospholipids and inserts into the cell membrane, facilitating membrane pore formation and pyroptotic cell death[42]. Additionally, GSDMD-N up-regulates the release of inflammatory mediators from macrophages recruited by monocyte chemotactic protein 1 and its receptor CC chemokine receptor-2[43]. This leads to an amplified inflammatory response, which in turn exacerbates ALF. NLRP3 could stimulate pyroptosis by inducing caspase-1 and GSDMD activation[18]. Furthermore, HMGB1 induces the formation of NLRP3 inflammasome by activating the TLR4/MyD88/NF-κB signaling pathway, thereby causing pyroptosis[44]. Studies have shown that IL-10 inhibits NLRP3 expression[45], suggesting a potential role for IL-10 in alleviating ALF. CD38, a type II transmembrane protein, is an important NAD-dependent enzyme, and it has been shown that CD38 stimulated TLR4-NLRP3-GSDMD-mediated pyroptosis and aggravated liver injury[46]. The occurrence of pyroptosis is influenced by multiple factors, which in turn impacts the progression of ALF, suggesting that the inhibition of pyroptosis could potentially alleviate ALF.

The regulation of deacetylases on ferroptosis and pyroptosis in ALF

In the study by Zhou *et al*[26], the authors suggested that SIRT1 activation reduced hepatic injury and inflammatory responses by reducing the p53 acetylation level and further suppressing the expression of ferroptosis and pyroptosis-related proteins GPX4 and GSDMD. SIRT1 is one of the important deacetylases, which could remove acetyl groups from histones and non-histone proteins. As protein acetylation is a crucial post-translational modification, we here review the regulation of deacetylases on ferroptosis and pyroptosis, and further on ALF.

SIRT1, which regulates the onset and progression of ALF by affecting ferroptosis and pyroptosis pathways[47] has received significant attention in recent years. The inhibitory effect of SIRT1-mediated deacetylation on ferroptosis is exerted through two major pathways: The deacetylation of p53 to suppress p53-dependent downregulation of SLC7A11[48], and the other pathway is the deacetylation of Nrf2 to promote Nrf2-mediated upregulation of GPX4[49]. In addition, SIRT1 could reduce the activation of NLRP3 inflammasome induced by IL-1β, thereby inhibiting pyroptosis[50]. Besides SIRT1, other deacetylases, such as HDAC6 and HDAC2 also have crucial actions in the regulation of ferroptosis and pyroptosis. For instance, studies have demonstrated that inhibition of HDAC6 expression reduced the expression of NLRP3 inflammatory vesicles and NF-κB, thereby affecting pyroptosis and ferroptosis in ALF, respectively[51,52]. Furthermore, downregulation of HDAC2 alleviates cell pyroptosis in ALF by regulating the acetylation level of the ULK1 K68 site[53].

In summary, it can be concluded that deacetylases could alleviate ALF by inhibiting both the ferroptosis and pyroptosis process. These results may provide new therapeutic targets for alleviating ALF.

CONCLUSION

ALF is a severe liver disease in clinical practice, which is accompanied by the rapid death of massive hepatocytes and multiple inflammatory outbreaks. Ferroptosis and pyroptosis are important cell death modes in ALF. Ferroptosis is the result of increased intracellular ROS due to iron accumulation, GSH depletion, and decreased GPX4 activity[54]. Pyroptosis is a procedural cell death mediated by the gasdermin family, which is dependent on the cleavage of GSDMD to the active GSDMD-N fragment by the NLRP3-induced caspases, and further triggering cell membrane perforation and an inflammatory storm[42]. Therefore, suppressing the ferroptosis and pyroptosis process has great potential in the treatment of ALF.

To date, some agents with iron removal or GPX4 regulating effects have shown ferroptosis-inhibitory functions. As iron ion accumulation is an essential prerequisite for ferroptosis, iron removal agents can be used to reduce the accumulation and deposition of iron in the organ and further mitigate the ferroptosis procedure. Iron chelators such as

deferoxamine, deferiprone and deferasirox have been proved to weaken lipid peroxidation by restricting the Fenton reaction, thereby inhibiting ferroptosis and alleviating ALF development[55]. GPX4 is a critical regulator of ferroptosis, thus enhancing the expression or the activity of GPX4 could inhibit this cell death mode. It was indicated that selenium supplementation could increase the level of GPX4 and inhibit ferroptosis as selenium is required for the synthesis of GPX4[56]. Multiple studies have shown that SIRT1 alleviates the inhibitory effects of p53 on GPX4 and SLC7A11 by reducing the level of p53 acetylation, which is a potential target for the treatment of ferroptosis-related diseases[57,58].

To date, a significant number of inhibitors and drugs targeting pyroptosis-related proteins have shown therapeutic potential in preclinical studies. As the activation of NLRP3 serves as the initiating point of pyroptosis, NLRP3-specific inhibitors have emerged as promising therapeutic targets for the treatment of pyroptosis, with MCC950 and the natural compound kaempferol currently undergoing clinical trials[59]. A study also pointed out that metformin, a "magic drug for diabetes treatment", could reduce inflammatory responses and cellular pyroptosis by inhibiting the NF-κB-NLRP3 pathway[60]. In addition, caspase inhibitors such as Vx765 and Z-YVAD-FMK block the binding of caspases to GSDMD and further inhibit pyroptosis[61]. Research has shown that the tricarboxylic acid cycle intermediate fumarate acts as a pyroptosis inhibitor by succinylating GSDMD to prevent its binding to caspases[62].

Although several candidates could be selected to regulate the critical steps in ferroptosis and pyroptosis, we still face many problems in clinics. For example, many existing inhibitors may interfere with normal metabolism pathways due to their nonspecific activity. The poor absorption rate of some drugs is another problem which needs to be resolved. With advances in science and technology, the use of big data and artificial intelligence methods to screen existing FDA-approved drugs may identify new ferroptosis and pyroptosis modulators. Existing studies have revealed that there is crosstalk between ferroptosis and pyroptosis through complex feedbacks, and the specific mechanism of the two cell death modes is still largely unknown, and the in-depth study of these pathways may provide targets and a theoretical basis for the development of ferroptosis and pyroptosis-targeted drugs.

FOOTNOTES

Author contributions: Sun YW and Zhao BW wrote the original draft, and revised the manuscript; Zhang GX wrote the original draft; Li HF supervised, conceived, verified, reviewed, and edited the manuscript. All authors were involved in the critical review of the results and have contributed to reading and approving the final manuscript. Sun YW and Zhao BW contributed equally to this work as co-first authors. The reasons for designating Sun YW and Zhao BW as co-first authors are twofold. First, the review was prepared as a collaborative effort with Sun YW and Zhao BW contributing equally to literature searching, draft writing, and manuscript revising. The designation of co-first authors authorship reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the review and ensure effective communication and management of post-submission matters. Second, Sun YW and Zhao BW are skilled in different fields, which promotes the most comprehensive and in-depth discussion of the review topic, ultimately enriching reader understanding by offering various expert perspectives.

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EDITORIAL

Glucagon-like peptide 1 receptor agonist: A potential game changer for cholangiocarcinoma

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Abstract

Glucagon-like peptide-1 receptor (GLP-1R) agonist, a subgroup of incretin-based anti-diabetic therapies, is an emerging medication with benefits in reducing blood glucose and weight and increasing cardiovascular protection. Contrarily, concerns have been raised about GLP-1R agonists increasing the risk of particular cancers. Recently, several epidemiological studies reported contradictory findings of incretin-based therapy on the risk modification for cholangiocarcinoma (CCA). The first cohort study demonstrated that incretin-based therapy was associated with an increased risk of CCA. Later studies, however, showed a null effect of incretin-based therapy on CCA risk for dipeptidyl peptidase-4 inhibitor nor GLP-1R agonist. Mechanistically, glucagon-like peptide 1 receptor is multifunctional, including promoting cell growth. High GLP-1R expressions were associated with progressive phenotypes of CCA cells *in vitro*. Unexpectedly, the GLP-1R agonist showed anti-tumor effects on CCA cells *in vitro* and *in vivo* with unclear mechanisms. Our recent report also showed that GLP-1R agonists suppressed the expression of GLP-1R in CCA cells *in vitro* and *in vivo*, leading to the inhibition of CCA tumor growth. This editorial reviews recent evidence, discusses the potential effects of GLP-1R agonists in CCA patients, and proposes underlying mechanisms that would benefit from further basic and clinical investigation.

Key Words: Carcinogenesis; Cholangiocarcinoma; Diabetes mellitus; Incretin; Glucagon-

like peptide 1 receptor

Core Tip: Glucagon-like peptide 1 receptor (GLP-1R) agonists, an anti-diabetic drug with other systemic benefits, have been reported for their association with increased risk of some cancers. Although the associations between GLP-1R agonists and the risk of cholangiocarcinoma (CCA) have not been consensus, the use of GLP-1R agonists showed the anti-tumor effects against CCA *in vitro* and animal models are evident. This editorial reviews and discusses recent studies of the effects of GLP-1R agonists both at epidemiological and molecular levels. The understanding of how GLP-1R agonist affects CCA will be beneficial for the management of patients with CCA and diabetes mellitus.

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INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive cancer of the biliary tract. Approximately 70% of patients with CCA were diagnosed at an advanced stage[1]. The incidence of CCA varies enormously globally, from 0.4 per 100000 in Canada to 85 per 100000 in northeastern Thailand, the highest incidence in the world[1,2]. According to the 8th Edition American Joint Committee on Cancer staging for Hepato-Pancreato-Biliary cancer, CCA is classified into 3 subtypes due to anatomical origin: Intrahepatic CCA, perihilar CCA, and distal CCA[3]. Several risk factors for the development of CCA have been identified, including liver fluke infections, biliary-tract disorders, hepatolithiasis, toxins, cirrhosis, chronic hepatitis B and hepatitis C infections, chronic alcohol consumption, diabetes mellitus (DM), and obesity[4].

Major risk factors for CCA differ greatly globally. At this point, DM is considered a minor risk. However, the DM burden is increasing significantly - the age-standardized prevalence of DM increased by 90.5% worldwide between 1990 and 2021[5]. Globally, the number of DM patients is expected to increase from 529 million in 2021 to 1.31 billion in 2050. In combination with carcinogenic liver fluke-*Opisthorchis viverrini* infection, DM has been shown to synergistically strengthen the association for the development of CCA[5,6]. Further, both CCA and DM exhibit high mortality rates in the CCA endemic regions in northeastern Thailand[7].

Previous studies have described molecular mechanisms linking DM to the development and progression of CCA[8]. The effects of insulin on increasing the risk of CCA are unclear, but the usage of exogenous insulin for DM treatment has shown an association with an increased risk of extrahepatic CCA[9]. The roles of insulin on CCA progression have yet to be clarified, although the expressions of insulin-like growth factor receptors[10] and insulin receptor substrate protein have been reported with prognostic roles in CCA[11,12]. On the other hand, our previous reports have clearly demonstrated that hyperglycemia or high glucose itself is a major contributor to CCA progression. High glucose activates multiple pro-tumorigenic signaling pathways in CCA cells, namely, Janus kinase 2/signal transducer and activator of transcription 3[13], nuclear factor-kappa B[13], glycogen synthase kinase-3β/β-catenin pathways[14]. Since glucose seems to be a key player in DM promoting CCA[15], anti-diabetic medications whose effects are to control blood glucose are therefore potentially involved in CCA development and progression, either promoting or retarding the cancer cells. One of the hypoglycemic agents that draw the attention of researchers in CCA biology is a glucagon-like peptide 1 receptor agonist[8].

GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONIST: EMERGING ANTI-DIABETIC AGENTS WITH QUESTIONABLE EFFECTS ON CANCERS

Glucagon-like peptide 1 receptors (GLP-1R) are expressed in many organs or tissues, such as the pancreas, thyroid, brain, and gastrointestinal tract. A primary effect of hypoglycemia relies on the activation by its ligand glucagon-like peptide 1 (GLP-1) at the pancreatic β cells. The activation of GLP-1R signals *via* Akt pathways to stimulate insulin secretion. The primary hypoglycemia effects are thus dependent on the actions of insulin, and additional anti-diabetic effects have also been reported[16]. A native GLP-1 itself, however, has low bioavailability and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4)[16]. DPP-4 inhibitors and analogs of GLP-1 have then been developed to increase the actions and the activation of GLP-1 and GLP-1R for the treatment of DM, called incretin-based therapy. They are globally recommended as a second or third-line treatment for type 2 DM as they possess some benefits for other systems, like weight control and cardiovascular benefits[17].

The primary effects of incretin-based therapy are *via* increasing insulin secretion. Since insulin is questioned for its roles in some cancer development, GLP-1R agonists have also been queried for their effects on tumor development and progression as well. In addition, the activation of GLP-1R mainly signals *via* the cascades of various pro-tumorigenic pathways, such as PI3K/Akt pathways[8]. These have led to investigations into the association between the use of GLP-1R agonists and the development of cancers. Nowadays, positive associations between using GLP-1R agonists and increased risk of thyroid cancers are widely reported[18-20], whereas other endocrine-related cancers, *e.g.*, breast and pancreatic cancers, have shown no association[19,21-24]. On the other hand, GLP-1R agonists use has been associated with reduced risk of prostate[18,25] and lung cancer[18].

GLP-1R AND GLP-1R AGONISTS: FRIENDS OR FOES OF CCA?

A large retrospective cohort study in the United Kingdom showed that DPP-4 inhibitors were associated with an increased risk of CCA[26]. However, the same study did not find any association between using GLP-1R agonists and the increased risk of this cancer. Since the hypoglycemic effects of DPP-4 inhibitors are passed through the bioavailability of GLP-1 and insulin, this might suggest that the effects of DPP-4 inhibitors are possibly associated with the other mechanisms. Although this was a large cohort study, it has limitations due to being an observational study. Also, the discrepancy between the effects of DPP-4 inhibitor and GLP-1R agonist suggested that the association between incretin use and increased risk of CCA might not be a direct effect of incretin-based therapy. Later, case-control studies conducted in Scandinavia[27] and Italy[28] consistently reported null effects for GLP-1R agonists on CCA risk. However, again limited by being observational studies in relatively smaller sample sizes, these latter studies could not totally exclude the possible risk of using GLP-1R agonists and CCA development.

A recent systematic review and meta-analysis of randomized control trials also found that although using GLP-1R agonists is significantly associated with the increased risk of benign biliary diseases, the increased risk of malignancy development in the biliary tract in GLP-1R agonist users was not different from the control groups[29]. This meta-analysis of randomized control trials strengthens the suggestion that GLP-1R agonists are potentially safe from increasing the risk of CCA in patients who use this drug group. To date, all epidemiological studies suggest that GLP-1R agonists are less likely to be associated with increased CCA risk. However, most studies were conducted in Western countries where the incidence of CCA is rare and is not associated with liver fluke infection. These different genetic and environmental backgrounds might confound study results, and more investigations that cover other ethnicities and regions would help clarify the effects of GLP-1R agonists on CCA development and the generalizability of results. The findings from epidemiological studies on GLP-1R agonists and the risk of biliary tract cancer/CCA are summarized in Table 1.

In addition to epidemiological evidence, molecular studies on GLP-1R and GLP-1R agonists indicate that using GLP-1R agonists may be beneficial for CCA treatment. GLP-1R is widely expressed in cholangiocytes and protects the biliary epithelium from cell apoptosis[30,31], which has led to the hypothesis that excessive activation of GLP-1R might promote the immortality of stimulated cells and increase the risk of cancer development[8]. Further, GLP-1R has also demonstrated pro-tumorigenic roles, as it controls the epithelial-mesenchymal transition and migration of CCA cells *in vitro* [32]. However, the roles of GLP-1R in CCA cells are not straightforward. An immunohistochemical study of GLP-1R expression in CCA tissues did not show any associations between expression levels and CCA patients' survival or other prognostic factors[33]. In contrast, another study activating GLP-1R by exendin-4 showed the opposite results in CCA cell lines. Exendin-4, a GLP-1R agonist with approximately 53% analogous to the human native GLP-1 peptide, suppressed CCA proliferation and induced chemosensitivity *in vitro* and *in vivo*[34]. Exendin-4 also exerted inhibitory effects against CCA metastatic potential by suppressing the migratory activity of CCA cells *in vitro* with unclear mechanisms. Our recent study also supports the findings of exendin-4's effects on CCA cells. Liraglutide, another GLP-1R agonist with a higher degree of analogy to native GLP-1, showed significant anti-tumor effects against intrahepatic CCA, partly by downregulation of GLP-1R[35]. In parallel to the downregulated GLP-1R expressions, our study also showed that Akt and STAT3 signaling pathways were suppressed in CCA after treatment with liraglutide *in vitro* and *in vivo*. Suppressing these signaling pathways thus resulted in the inhibition of growth and epithelial-mesenchymal transition of CCA cells. However, whether liraglutide exhibiting anti-tumor effects on CCA cells is GLP-1R dependent or independent and whether liraglutide affects other subtypes of CCA needs further investigation. Further, investigating the effects of other GLP-1R agonists in CCA patients with different genetic backgrounds would also help clarify existing epidemiological findings.

In summary, all the data from *in vitro* and *in vivo* studies suggest that even though GLP-1R has pro-tumorigenic roles, using GLP-1R agonists may not result in higher aggressive phenotypes of CCA cells. On the other hand, GLP-1R agonists seem beneficial for CCA treatment, but the underlying mechanisms are not fully understood. In addition, there is a lack of cohort or randomized control trial studies of the association between using GLP-1R agonists and the prognosis in patients with CCA and DM. These contradictions need further investigation, not only for the proper management of patients with CCA and DM but also for a possible repurposing of GLP-1R agonists for CCA add-on treatments.

CONCLUSION

At present, evidence indicating an association between GLP-1R agonist usage and the increased risk of biliary tract cancer and CCA is unclear. Pro-tumorigenic roles of GLP-1R in CCA have been reported; however, the benefits of using GLP-1R agonists in CCA treatment *in vitro* and *in vivo* are also evident. Based on previous studies, using GLP-1R agonists to treat

Table 1 Epidemiological studies on associations of glucagon-like peptide-1 receptor agonist and risk of cholangiocarcinoma

Ref.	Region of study	Study design	Results (95%CI)
Abrahami *et al*[26], 2018	United Kingdom	Cohort study	HR: 1.97 (0.83-4.66)
Giorda *et al*[28], 2020	Italy	Case-control study	OR: 1.09 (0.63-1.89)
Ueda *et al*[27], 2021	Scandinavia	Cohort study	HR: 1.25 (0.89-1.76)
He *et al*[29], 2022	Worldwide	Systematic review and meta-analysis	RR: 1.43 (0.80-2.56)

HR: Hazard ratio; OR: Odds ratio; RR: Risk ratio.

DM might still be safe and beneficial for those who have underlying CCA.

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FOOTNOTES

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EDITORIAL

Examining dietary interventions in Crohn's disease

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Abstract

This editorial builds on the article by Shakhshir *et al*. We conducted an overview of evidence-based dietary interventions in adults with inflammatory bowel disease (IBD). In the IBD population, there may be a role for the Mediterranean diet due to its anti-inflammatory effects, long-term sustainability, and role in improving cardiovascular health. In active Crohn's disease, the use of exclusive enteral nutrition, the Crohn's disease exclusion diet, or the specific carbohydrate diet may be used as a short-term adjunct to medical therapy and may improve mucosal healing. The low-FODMAP diet can assist in reducing symptoms for patients without evidence of active bowel inflammation. As interest in nutritional therapy increases amongst clinicians and patients alike, it is integral that dietary therapies are understood and discussed in routine management of patients with IBD as part of holistic care, ideally through a multidisciplinary setting with involvement of experienced dietitians. This serves to improve clinician-patient engagement and reduce complications of IBD including micro and micronutrient deficiencies.

Key Words: Inflammatory bowel disease; Nutrition; Dietary therapies; Inflammation; Malnutrition

Core Tip: Dietary therapies can be used to reduce inflammation or improve symptoms in patients with Crohn's disease. The Mediterranean diet has been associated with improved outcomes in inflammatory bowel disease (IBD), and potentially reducing its development. Exclusive enteral nutrition and Crohn's disease exclusion diet can be used for the induction of remission in Crohn's disease. Multidisciplinary management of patients with IBD should include dietary advice and the involvement of experienced dietitians.

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INTRODUCTION

This editorial comments on the article 'Global research trends on diet and nutrition in Crohn's disease' by Shakhshir *et al* [1]. Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic remitting and relapsing conditions of the gastrointestinal tract characterised by inflammation and an aberrant immune response[2]. The aetiology of IBD is postulated to involve a complex interplay between environmental and genetic factors[3]. Among the environmental factors, dietary factors have been implicated, including the use of dietary emulsifiers, poly-unsaturated fats, and ultra-processed foods[4,5]. Nutritional interventions are increasingly recognised as a critical component of comprehensive IBD care, encompassing strategies to mitigate disease symptoms, reduce inflammation, and correct nutritional deficiencies. Malnutrition is a significant concern in IBD patients due to factors such as poor gastrointestinal absorption, increased gastrointestinal losses, and a hypermetabolic state driven by chronic inflammation. These factors contribute to a high prevalence of micronutrient and macronutrient deficiencies, which can exacerbate disease related symptoms and impair patient reported quality of life[6,7].

As identified by Shakhshir *et al*[1], there is growing interest in dietary approaches in treating Crohn's disease with a steady growth of publications in this field, however, further knowledge is required to strengthen recommendations in nutrition management in IBD. Landmark dietary trials in paediatric populations have been extrapolated for use in adult populations, however the role of dietary therapies is less certain given the presence of more heterogenous disease phenotype and variability in lifestyles. Hence, an awareness of the role and effectiveness of dietary therapies in IBD remains integral in making evidence-based recommendations to patients for managing IBD. This editorial focuses on the role of diet in Crohn's disease in the adult population, as its efficacy in ulcerative colitis is less certain.

ROLE OF DIET IN PATHOGENESIS AND AETIOLOGY

The multifactorial aetiology of IBD involves a dynamic interplay between genetic predisposition, environmental factors, immune dysregulation, and gut microbiota alterations. Among these, diet has emerged as a crucial environmental factor influencing the development and progression of IBD.

Epidemiological studies have consistently shown that dietary patterns can influence the pathogenesis of IBD[4]. In fact, Western dietary patterns characterised by high intake of refined sugars, fats, and processed foods and low intake of fibre have been associated with an increased IBD risk and more active disease[4]. Conversely, diets rich in fibre, fruits, vegetables, and anti-inflammatory nutrients such as omega-3 fatty acids and vitamin D have been associated with a lower risk of IBD[8].

The role of short-chain fatty acids, such as butyrate; a product of fermentation of dietary fibres with anti-inflammatory properties, is hypothesised to play a role in maintaining intestinal barrier integrity and gut homeostasis[9]. Studies also show that patients with IBD have lower levels of faecal short-chain fatty acids[9,10]. Dietary fats, including polyunsaturated fatty acids and omega-6 fatty acids from animal protein, excluding eggs and dairy, have also been implicated in incident cases of IBD[11].

PATIENT AND CLINICIAN PERCEPTIONS

As a modifiable lifestyle factor, diet presents an attractive therapeutic option due to its potential to improve quality of life with fewer perceived side effects than medical therapy. Moreover, patients often proactively initiate dietary modification, including self-restrictive diets, to manage their symptoms. In large scale questionnaires, up to two-thirds of patients report avoiding foods they enjoy to help prevent relapse of IBD[12] and majority (85.4%) of patients believed that diet triggers relapses[13]. Similarly, 59% of patients valued nutrition to be at least as important as pharmacotherapy for the management of IBD, including 62% who believed diet to be more important in influencing the disease course[14].

In addition, nearly half (43.8%) of patients describe dietary modifications, whether self-adjusted or clinician prescribed, to have significant interference in their social life[15]. From the clinicians' perspective, diet is increasingly recognised as

an adjunctive treatment to pharmacotherapy, and dietitians can play a pivotal role in multidisciplinary management of IBD when they are available. The lack of high-quality trials and scarcity of practical resources can limit the use of dietary therapies, with only a limited number of gastroenterologists actively incorporating dietary counselling into clinical practice[16].

Further work is required to bridge the gap between patient and clinician perceptions towards dietary therapy in IBD. A cross-sectional study of 928 patients found that 61% of patients felt their IBD specialist disregarded the importance of diet in their management. Only 26% reported receiving dietary advice from their doctor despite nearly all (98%) gastroenterologists surveyed reporting providing advice[17].

A key strategy is the inclusion of an experienced dietitian as standard of care in IBD management. Dietitians play an important role in the assessment and can tailor individualised plans in approaching malnutrition management, instituting therapeutic diets and alleviating symptoms[18].

MEDITERRANEAN DIET

The Mediterranean diet (MD), characterised by high consumption of fruits, vegetables, whole grains, legumes, fish, and olive oil, and low intake of red meat and processed foods, is the hallmark of lifestyle modifications and diet therapy in cardiovascular and metabolic health. It is associated with lower levels of systemic inflammation and oxidative stress markers in the general population[19,20].

MD's dietary plan shares similarities with foods that have been implicated as protective factors and aims to avoid foods that have been implicated as risk factors for the development of IBD. A large-scale prospective cohort study has shown a lower risk of Crohn's disease onset (HR = 0.42, 95%CI: 0.22-0.80) in participants adherent to the MD, but not ulcerative colitis (HR = 1.08, 95%CI: 0.74-1.58)[21].

In patients with active Crohn's disease, the MD has shown similar rates of remission as induction therapy compared to the specific carbohydrate diet (SCD). A randomised trial involving patients with ileal (23.9%), colonic (17%), and ileocolonic (57.6%) disease showed 43.5% of the MD group achieving symptom remission at week 6, compared to 46.5% in the SCD group (P = 0.77). Faecal calprotectin response was not significantly different between the two groups (MD 30.8% *vs* SCD 43.88%; P = 0.83. Both diets were well tolerated, however adherence to a strict diet declined over time to 40% at week 12[22]. A randomised control trial of ulcerative colitis patients saw similar improvements in faecal calprotectin compared to an unrestricted diet (20% FC > 100 *vs* 75% FC > 100), with good tolerability[23].

EXCLUSIVE ENTERAL NUTRITION

Exclusive enteral nutrition (EEN) has emerged as a compelling therapeutic option in inducing remission and mucosal healing in Crohn's disease without several of the adverse effects associated with pharmacotherapy. EEN involves the exclusive consumption of a nutritionally complete liquid formula while eliminating regular solid food intake. Common regimes include a six to eight week period of exclusive use following which a normal diet is gradually reintroduced. The mechanisms by which EEN exerts its beneficial effects are hypothesised to be related to modulation of the gut microbiota, reduction of intestinal permeability, anti-inflammatory effects, and providing bowel rest which could contribute to mucosal healing[16,24].

Several clinical trials have established EEN as an effective first-line therapy for inducing remission in Crohn's disease. A randomised controlled trial by Borrelli *et al*[25] demonstrated that a polymeric diet was more effective than corticosteroids (79% *vs* 67%) in inducing healing in a paediatric population. Subsequent studies have supported these findings showing improvement in biochemical and endoscopic response rates and nutritional parameters without side effects[26-29].

In adult populations, the data is less robust and larger studies have not been able to recreate the same degree of efficacy. A meta-analysis demonstrated that EEN was not superior in efficacy to steroids as induction therapy in an adult population, with adverse events including nausea, vomiting, diarrhoea and bloating. Palatability and inability to tolerate EEN with symptoms of nausea, vomiting and fatigue were common reasons for withdrawal[30,31]. Early reports suggested greater efficacy with small bowel involvement whereas data on isolated colonic disease remains equivocal. Xu *et al*[32] described a 51.9% clinical remission rate in colonic Crohn's compared to 68.2% with ileal involvement.

Dissatisfication with not being able to eat food, especially on social occasions, also contributed to poor adherence[33]. This highlights that the implementation of EEN can be challenging, and adherence can be difficult over extended periods.

EEN can also be used as a steroid-sparing therapy, including as an adjunctive therapy to optimise nutrition and reduce post-operative complications in malnourished patients prior to elective IBD related bowel surgery, or for refractory disease in conjunction with medical therapy[34].

CROHN'S DISEASE EXCLUSION DIET

The Crohn's disease exclusion diet (CDED) is a structured diet that aims to reduce gut inflammation by excluding certain foods known to exacerbate symptoms and possibly trigger immune responses and gut dysbiosis. This diet focuses on eliminating specific food components, such as gluten, dairy, processed foods, and certain additives, while encouraging

the consumption of fruits, vegetables, lean proteins, and other nutrient-dense foods.

A study of forty-four adults with mild-moderate Crohn's disease showed 57% clinical remission at week 6, and 68% when combined with partial enteral nutrition. Eighty percent of those in remission at week 6 maintained clinical remission at week 24, with 35% in endoscopic remission at the time[35]. Earlier paediatric studies demonstrated an increase in steroid-free remission in patients with CDED, with augmentation of the effect when partial enteral nutrition was added[24,36].

One of the key strengths of the CDED is its ability to provide balanced and adequate intake of essential nutrients unlike highly restrictive diets that may lead to nutritional deficiencies. The CDED is implemented in phases, allowing for gradual reintroduction of excluded foods. This phased approach helps in identifying specific dietary triggers and maintaining long-term adherence.

CDED provides a good alternative where there is intolerance to EEN with improved compliance (85% *vs* 63%)[35]. Consensus agreements recommend supplementation with enteral nutrition to meet nutritional requirements and diet reintroduction after 12 weeks of therapy to avoid malnutrition[37].

SCD

The SCD is a nutritional regimen that restricts the intake of complex carbohydrates, and promotes the consumption of monosaccharides, which are easily absorbed and purported to minimise microbial dysbiosis. It is based on the theory that certain carbohydrates are not completely digested and absorbed, leading to fermentation and growth of pathogenic bacteria in the intestines.

In the paediatric populations with Crohn's disease, studies have observed clinical and laboratory improvements following SCD therapy as well as significant changes in the faecal microbiome[38,39]. Use of the SCD has been shown to increase populations of beneficial bacteria and decrease inflammatory markers in a paediatric population with active Crohn's disease[40]. A randomised trial comparing SCD with the MD in adult patients with Crohn's disease found similar rates of early remission at week 6 (46.5% *vs* 43.5%) with a faecal calprotectin reduction in 34.8% and 30.8% respectively[22]. However, there are limited controlled studies comparing SCD to an unrestricted diet, limiting its widespread take-up as first-line dietary therapy in IBD.

Potential drawbacks from using the SCD long-term include its restrictive nature given elimination of sugars, high-lactose dairy and starchy vegetables.

LOW-FODMAP DIET

The low FODMAP diet, initially developed for the management of irritable bowel syndrome (IBS), has increasingly been examined for its potential benefits in patients with IBD. This dietary intervention focuses on reducing the intake of carbohydrates that are poorly absorbed in the small intestine and highly fermentable, potentially exacerbating symptoms like bloating, gas, and abdominal pain through luminal distension and altered gut motility[41]. Given the overlap in symptoms between IBS and IBD, particularly during quiescent phases of the latter, the low FODMAP diet has been considered a valuable nutritional approach for symptom management in IBD patients.

Low FODMAP diet was beneficial for symptom management in IBD, with approximately half of patients finding improvement in symptoms of abdominal pain, bloating, wind, and diarrhoea. Compliance can be a limiting factor in its widespread use and lower compliance has been associated with a lack of efficacy[42-44]. A systematic review of 319 patients in IBD (96% in remission) found a significant improvement in diarrhoea, satisfaction of gut symptoms, bloating, pain, fatigue; however did not improve constipation[45].

The role of the low FODMAP diet on long-term disease outcomes and inflammation remains under investigation and it currently cannot be recommended as a treatment of IBD but rather as an adjuvant treatment for symptomatic improvement. Furthermore, it may not be suitable for those with severe disease due to the risk of nutrient deficiencies and potential impact on disease activity. Its sustainability can be challenging due to its restrictive nature, with long-term adherence diminishing over time.

MICRONUTRITON and MACRONUTRIENTS

Reduced dietary intake due to anorexia, nausea, and abdominal pain, combined with malabsorption and increased metabolic demands, contribute to macronutrient and energy deficits. Comprehensive nutritional assessment, including regular monitoring of body weight, body composition, and laboratory markers of nutritional status, is essential for identifying and addressing nutrient deficiencies in IBD patients. The use of screening tools such as the Malnutrition Universal Screenng Tool, Saskatchewan IBD-nutrition risk and Subjective Global Assessment can help clinicians identify at-risk patients and tailor nutritional interventions accordingly[46,47]. A cross-sectional study of over 200 patients with IBD found malnutrition rates of 27%-37%[48].

Iron deficiency is prevalent due to chronic intestinal bleeding, reduced iron absorption, and inflammation-induced alterations in iron metabolism. Routine screening allows for early detection, and management with intravenous iron therapy is shown to be more effective and better tolerated than oral iron[49,50]. Low vitamin D levels are associated with

increased disease activity and a higher risk of hospitalisation and surgery in IBD patients, highlighting the need for regular monitoring and supplementation[51]. A prospective study showed low micronutrient levels were common even in quiescent disease; vitamin D was the most common deficiency (29%), followed by zinc (16%), vitamin B6 (14%), vitamin C (13%) and vitamin B12 (11%)[52]. Folate and vitamin B12 deficiencies are also common, especially with ileal Crohn's or post-ileal resection[53]. Regular monitoring and supplementation of these vitamins were necessary to prevent anaemia and neurological complications.

CLINICAL IMPLICATIONS

The role of diet in IBD is increasingly recognised as an area of importance by clinicians and patients alike. This is an evolving field so there may be disparities in perceptions and attitudes toward diet between patients and clinicians which may partially relate to differences in how information is acquired. For example, patients may revert to social media, online forums, and patient advocacy groups for dietary advice while clinicians may rely on peer-reviewed journals, clinical guidelines, and professional societies for guidance. Improved awareness, communication and education, the development of evidence-based dietary guidelines, and the inclusion of dietitians in IBD care are integral steps in bridging this gap so that nutritional therapy can be optimised for patients with IBD.

CONCLUSION

Dietary therapies are an important element of IBD management. It can provide wide ranging benefits in improving nutritional outcomes, alleviating symptoms and sometimes improving inflammation. Evidence supports the integration of nutritional care into standard IBD management protocols, emphasising the need for multidisciplinary approaches that include dietitians and nutrition specialists. As further research and interest grows, integrating dietary knowledge and therapies in IBD care is adding to the potential strategies for optimising outcomes in IBD.

FOOTNOTES

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EDITORIAL

Editor-in-Chief articles of choice and comments from January to June 2024

Andrzej S Tarnawski

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade A, Grade B

Scientific Significance: Grade B, Grade C

P-Reviewer: Shahidi N; Teng X

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Abstract

As the Editor-in-Chief of the *World Journal of Gastroenterology*, I carefully review all articles every week before a new issue's online publication, including the title, clinical and research importance, originality, novelty, and ratings by the peer reviewers. Based on this review, I select the papers of choice and suggest pertinent changes (*e.g.*, in the title or text) to the company editors responsible for publication. This process, while time-consuming, is essential for assuring the quality of publications and highlighting important articles that readers may revisit.

Key Words: Papers of choice; Weekly review; Suggested changes/revisions; Hepatocellular carcinoma; Pancreatic cancer; Liver cirrhosis; Liver injury; Gastric cancer; Colorectal cancer; Inflammatory bowel diseases

Core Tip: Every week before a new issue's online publication, I perform a careful review of all articles, including the title, originality, novelty, and ratings by the peer reviewers. Based on this review, I select the papers of choice, suggest pertinent changes (*e.g.*, in the title), and share my comments with the company editors responsible for publication. This process is critical for assuring the quality of publications and highlights important articles that readers may revisit.

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INTRODUCTION

Prestigious posts such as those of the Editor-in-Chief of the *World Journal of Gastroenterology* (*WJG*) come with duties. Every week before a new issue's online publication, I carefully review all articles, including the title, clinical and research importance, originality, novelty, and ratings by the peer reviewers. Based on this review, I select my papers of choice, suggest changes (*e.g.*, in the title), and share my comments with the company editors responsible for publication. While time-consuming, this process is essential for assuring the quality of publications and highlighting important articles that Readers may revisit. Overall, the reviewers performed careful peer reviews. In addition, *WJG* Scientists and the Company Editor-in-Chief performed additional reviews and evaluations, ensuring the papers' quality is good.

HOT ARTICLES-ARTICLES OF CHOICE AND OTHER ARTICLES

Gastroenterology and hepatology

***WJG*v30i1:** This issue contains 10 articles, including 2 editorials, 2 articles related to the liver and 2 letters to the editor. The articles in this first 2024 issue are very interesting and represent a good start to a New Year 2024.

I especially like papers: (1) "May ChatGPT be a tool producing medical information for common inflammatory bowel disease patients' questions? An evidence-controlled analysis[1]". This article presents a new important tool for the patients and health care professionals; (2) 2023: A year of accomplishments for the 13 Science Citation Index Expanded- and Emerging Sources Citation Index-indexed Baishideng journals[2]. It is very useful, especially for the academic gastroenterologists, hepatologists and surgeons; and (3) Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction: An exploratory proposal based on basic and clinical data[3]. This paper presents a new hypothesis and a novel concept with potential science and clinical implications.

The reviewers performed overall very good peer reviews.

***WJG*v30i2:** This issue contains 8 articles, including one related to the liver.

Some articles are exciting and important. I especially like papers: (1) "Small nucleolar RNA and its potential role in the oncogenesis and development of colorectal cancer[4]." In my opinion, this article will stimulate research in the small nucleolar RNA area related to other cancers; (2) "Hepato-cardio-renal syndrome in liver cirrhosis: Recognition of a new entity?[5]" This is an interesting article proposing the important role of the heart in hepatorenal syndrome. This new term was used only once before and was cited by the authors. Reviewer #: 05230210 performed an excellent peer review, and his comments assisted the authors in strengthening this paper; and (3) "Association of tumor budding with clinicopathological features and prognostic value in stage III-IV colorectal cancer[6]". I fully agree with the reviewer's remarks: "Tumor budding is an exciting topic". It is not entirely new since a consensus in 2016 was released. However, this work provides important information regarding the significance of tumor budding in Stage III and IV colorectal cancer patients and how Bd2-3 are significant prognostic markers".

In the paper "Long-term prognosis and its associated predictive factors in patients with eosinophilic gastroenteritis[7]", reviewer 00058401 rated the article's scientific quality as grade C, but in SPECIFIC COMMENTS TO AUTHORS wrote only one word, "Congratulation". This is not a serious review.

Editor's reply: The author has been invited to provide a new response to the reviewer's comments and upload it to the system.

***WJG*v30i4:** This issue contains 9 articles, including 4/5 related to the liver.

The articles are interesting and important. I especially like papers: (1) "Revolutionizing gastric cancer treatment: The potential of immunotherapy[8]". This article will, in my opinion, stimulate research in this area and will be appreciated by the readers; (2) "Value of multiple models of diffusion-weighted imaging to predict hepatic lymph node metastases in colorectal liver metastases patients[9]"; and (3) Hepatic arterial infusion chemotherapy with anti-angiogenesis agents and immune checkpoint inhibitors for unresectable hepatocellular carcinoma and meta-analysis[10]. Please correct "inhibitiors" to inhibitors. It would be nice if the authors mention that Avastin is only the beginning for a new line of anticancer treatments that marks Napoleone Ferrara's long track record of discoveries from the identification of VEGF and its receptors, and their role in angiogenesis to the development of a viable drug–Avastin, Bevacizumab.

Since June 2023 the AASLD changed the nomenclature; namely, nonalcoholic fatty liver disease (NAFLD) was named metabolic dysfunction-associated steatotic liver disease (MASLD). The MASLD nomenclature encompasses patients who have hepatic steatosis and have at least one of five cardiometabolic risk factors. Please see: https://www.aasld.org/new-masld-nomenclature.

My question to the *WJG* Editors-do we wish to change and adopt this new nomenclature to *WJG*?

Editor's reply: Thank you for your comments. We will correct the typo in manuscript title "Hepatic arterial infusion chemotherapy with/without anti-angiogenesis agents and immune checkpoint inhibitiors for unresectable hepatocellular carcinoma and meta-analysis". And I have written to authors to ask for response to your comments.

In addition, I noticed it the second time you remind us the new nomenclature for nonalcoholic fatty liver disease, I will forward it to my colleague to discuss.

***WJG*v30i5:** This issue contains 10 articles, including 4 articles related to the liver and 2 letters to the editor. The articles in this issue are interesting.

I especially like papers: (1) "Leveraging machine learning for early recurrence prediction in hepatocellular carcinoma: A step towards precision medicine[11]". As the second reviewer pointed out this study is innovative, and may have certain value in the early recurrence of hepatocellular carcinoma after surgery. The model's ability to stratify risk facilitates targeted postoperative strategies, showcasing its potential as a guide for personalized patient care; and (2) "Development and validation of a prediction model for early screening of people at high risk for colorectal cancer[12]". The issue is clinically important.

The reviewers performed overall very good peer reviews.

***WJG*v30i7:** This issue contains 16 articles, including 2 editorials, 6 articles related to the liver and 2 letters to the editor. In this issue we have numerous very interesting articles.

I especially like papers: (1) "Pathophysiology of severe gallstone pancreatitis: A new paradigm[13]". This article provides basis for of the two types of biliary pancreatitis; (2) "Muscle strength and non-alcoholic fatty liver disease/metabolic-associated fatty liver disease[14]". The article is appealing and important by indicating that the hand-grip test is a suitable method and easily available tool for estimating someone's muscle strength and different health-related outcomes. It is also easily accessible in the population; and (3) "Erlotinib combination with a mitochondria-targeted ubiquinone effectively suppresses pancreatic cancer cell survival[15]". While *in vivo* importance of this cancer cell study is not certain, from the basic point of view the studies are important and promising.

The article "Metformin and pancreatic neuroendocrine tumors: A systematic review and meta-analysis[16]" the paper was reviewed by only 1 reviewer and no review was provided.

***WJG*v30i9:** This issue contains 22 articles, including 2 editorials, 11 articles related to the liver and 3 letters to the editor. The articles in this issue are very interesting. It took time to review them.

I especially like the following articles: (1) Title: "Role of exosomal circular RNAs as microRNA sponges and potential targeting for suppressing hepatocellular carcinoma growth and progression[17]". This article presents a new potentially important therapy; (2) Title: "From liver to hormones: The endocrine consequences of cirrhosis[18]". This is an interesting reminder for the readers; (3) Title: "Telomerase-related advances in hepatocellular carcinoma: A bibliometric and visual analysis[19]" An interesting update; and (4) Title: "PRaG 3.0 therapy for human epidermal growth factor receptor 2-positive metastatic pancreatic ductal adenocarcinoma: A case report[20]". An important potential therapy for this deadly disease.

The reviewers performed overall good peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i10:** This issue contains 20 articles, including 6 editorials, 5 articles related to the liver and 3 letters to the editor. All articles in this issue are interesting.

I especially like the following papers: (1) Title: Capsule endoscopy and panendoscopy: A journey to the future of gastrointestinal endoscopy[21]. Authors point that the horizons of capsule endoscopy are evolving. PCE is a non-invasive, effective, and safe procedure to evaluate the small bowel and the colon. Its use in CD and more recently in GI bleeding is expanding in routine clinical practice and offers the opportunity to evaluate multiple segments of the digestive tract at the same time, in a single non-invasive procedure. Currently, clinical indications for PCE include the assessment of non-stricturing, non-penetrating and extensive CD (affecting the small bowel and colon), mainly for disease monitoring and evaluation of mucosal healing in response to medical therapy; (2) Title: Vonoprazan-amoxicillin dual regimen with Saccharomyces boulardii as a rescue therapy for *Helicobacter pylori*: Current perspectives and implications[22]; (3) Title: Optimizing nutrition in hepatic cirrhosis: A comprehensive assessment and care[23]; and (4) Title: Stage at diagnosis of colorectal cancer through diagnostic route: Who should be screened?[24]. This article relates to a very important issue and an identified population that will benefit most from the screening.

The reviewers performed overall good peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i13:** This issue contains 13 articles, including 4 editorials, 5 articles related to the liver. The articles in this issue are very interesting and well selected.

I especially like the following papers: (1) Title: "History of chronic gastritis: How our perceptions have changed"[25]. This review paper is very well structured and provides in depth insight into and diagnosis of gastritis in time related manner; (2) Title: Molecular insights into clinical trials for immune checkpoint inhibitors in colorectal cancer: Unravelling challenges and future directions[26]. This paper may serve for developing of new therapies; and (3) Real-world efficacy and safety of tofacitinib treatment in Asian patients with ulcerative colitis[27]. This is a review on a new drug in UC studied in Asian patient.

The reviewers performed overall good peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i15:** This issue contains 11 articles, including 5 editorials, 5 articles related to the liver and 1 letter to the editor. All articles in this issue are very interesting.

I especially like the following papers: (1) Title: "Combination treatment of Inflammatory Bowel Disease: Present status and future"[28]. This is a clinically important issue; (2) Title: "Probiotics: Shaping the gut immunological responses"[29]. Very detailed and systematic review; and (3) OSW-1 triggers necroptosis in colorectal cancer cells through the RIPK1/RIPK3/MLKL signaling pathway facilitated by the RIPK1-p62/SQSTM1 complex[30]. This study provided a new mechanism.

Regarding paper: "Understanding autoimmune pancreatitis: Clinical features, management challenges, and association with malignancies[31]". In the abstract, the authors stated "In this editorial we comment on the article by Jaber *et al*." If this is the main point of the paper, this article should be the letter to the editor and not an editorial. The reviewer commented on this and was also annoyed by this statement. To correct the authors should delete this statement from the abstract and use it in the discussion.

In some papers medical English wording is not precise and reminds Google translation. In several articles detailed reviews are missing and only is a brief summary statement.

The reviewers performed overall good peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i16:** This issue contains 12 articles, including 2 letters to the editor. All articles in this issue are well selected and interesting.

I especially like the following papers: (1) Title: "Drug-induced mucosal alterations observed during esophagogastroduodenoscopy"[32]. I agree with the reviewer, who pointed out "that the author sorted out the classification and endoscopic manifestations of upper gastrointestinal mucosal injuries" and "This paper provides a reference basis for endoscopists to make diagnoses and it is helpful and useful in the clinic." The illustrations are of excellent quality; and (2) Title: "Laryngopharyngeal reflux disease: Updated examination of mechanisms, pathophysiology, treatment, and association with gastroesophageal reflux disease"[33]. Both reviewers rated this paper as "very good" and I fully agree, because this paper meticulously dissects the mechanisms of laryngopharyngeal tissues injury by different reflux substances such as hydrochloric acid, bile, gastric enzymes. In my opinion, this review provides better understanding of this complex medical condition.

The reviewers performed overall good peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i17:** This issue contains 12 articles, including 5 editorials, 6 articles related to the liver and 2 letters to the editor. The articles in this issue are very interesting.

I especially like the following papers: (1) Title: "Quick and easy assessment of sarcopenia in cirrhosis: Can ultrasound be the solution?"[34]. The reviewer pointed out that the authors should explain the term US. Also, the language should be more polished *e.g.*, US is "a cheap and harmless technique" should be substituted with" inexpensive and noninvasive procedure" or similar; (2) Title: "Contrast-enhanced guided endoscopic ultrasound procedures"[35]; and (3) Title: "Minocycline in the eradication of *Helicobacter pylori* infection: A systematic review and meta-analysis"[36].

The reviewers performed careful peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i18:** I read the articles and reviewers peer reviews with a great interest. This May 14 issue contains 13 articles, including 9 articles related to the liver and 3 letters to the editor. The articles in this issue are very interesting and important.

I especially like the following papers: (1) Title: "Metabolic dysfunction-associated steatotic liver disease: Navigating terminological evolution, diagnostic frontiers and therapeutic horizon-an editorial exploration"[37]. As pointed by the reviewer, this article explains nomenclature changes, diagnostic innovations, therapeutic possibilities, and the role of the microbiome. Perhaps the authors should elaborate on Resmetirom (Rezdiffra-approved by the FDA) that is a partial agonist of thyroid hormone receptor beta (THR-β) and works by preventing the liver from forming fat. THR-β is the main form of THR in the liver, and stimulation of it reduces triglycerides within the liver. The authors can add this in a subsequent letter to the editor as a follow up; (2) Title: "Endo hepatology: Arrival at the frontier of interventional endosonography"[38]. This article elaborates on new important direction; and (3) Title: "FibroScan-aspartate transaminase: A superior non-invasive model for diagnosing high-risk metabolic dysfunction-associated steatohepatitis"[39].

The reviewers performed overall good peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i19:** This issue contains 13 articles, including 4 articles related to the liver and 2 letters to the editor. The articles in this issue are interesting.

I especially like the following papers: (1) Title: "Immunotherapy for esophageal cancer: Where are we now and where can we go"[40]. The authors should specify in the title squamous esophageal cancer; and (2) Title: "Hepatocellular carcinoma-the role of the underlying liver disease in clinical practice"[41].

The reviewers performed careful peer reviews. Some articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation.

***WJG*v30i20:** This issue contains 12 articles, including 3 editorials, 7 articles related to the liver and 2 letters to the editor. The articles in this issue are very interesting.

I especially like the following papers: (1) Title: "Excess non-COVID-19-related mortality among inflammatory bowel disease decedents during the COVID-19 pandemic"[42]. Important conclusions; and (2) Title: "Development and validation of a new prognostic model for patients with acute-on-chronic liver failure in intensive care unit"[43]. Clinically important article.

In article "Exosomal microRNAs in hepatocellular carcinoma, rising research filed in hepatocellular carcinoma" instead of "filed" should be "field". I suggest changing the title to "Exosomal microRNAs in hepatocellular carcinoma, expanding research field"[44].

The reviewers performed careful peer reviews. Most articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation, which assured good quality of papers.

***WJG*v30i21:** This issue contains 10 articles, including 4 editorials, 2 articles related to the liver and 1 letter to the editor. The articles in this issue are very interesting.

I especially like the following papers: (1) Title: "Effects of proton pump inhibitors on inflammatory bowel disease: An updated review"[45]. Important clinical conclusions; and (2) Title: "Thymoquinone affects hypoxia-inducible factor-1α expression in pancreatic cancer cells *via* HSP90 and PI3K/AKT/mTOR pathways"[46]. Important basic article.

The reviewers performed careful peer reviews. Most articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation, which assured good quality of papers.

***WJG*v30i22:** This issue contains 12 articles, including 5 editorials, 6 articles related to the liver and 2 letters to the editor. The articles in this issue are very interesting and the choice of outstanding papers was difficult.

I especially like the following papers: (1) Title: "Histopathological impact of SARS-CoV-2 on the liver: Cellular damage and long-term complications"[47]. Important article. The reviewer provided excellent suggestions that markedly improved this paper; (2) Title: "Heparin is an effective treatment for preventing liver failure after hepatectomy"[48]. Important clinical article with potential therapeutic implications; and (3) Title: "Approach to loss of response to advanced therapies in inflammatory bowel disease"[49]. Important clinical article with potential therapeutic implications.

In the letter to the editor: "Interaction between inflammatory bowel disease, physical activity, and myokines: Assessment of serum irisin levels"[50] the reviewer did an excellent review. He stated *"I just want to know if the author's purpose of writing this letter is a suggestion or addition to Stafie et al.'s article? Or is it just a way of stating their opinion if they have a different opinion? Secondly, the quality of the author's pictures is very poor and there are paragraph marker symbols in the pictures, so I hope the author will make changes"*. I fully agree with this straightforward review.

Overall, the reviewers performed careful peer reviews. Most articles had only 1 reviewer, but *WJG* Scientists and Company Editor-in-Chief performed additional reviews and evaluation, which assured good quality of papers.

***WJG*v30i23:** This issue contains 10 articles (including 6 editorials, 1 review, 2 retrospective studies and 1 prospective study.

The article: "Close relationship between mediators of inflammation and pancreatic cancer: Our experience[51]". While the article sounds interesting, it has only Abstract, Introduction and Conclusion. The major parts, such as methods, results and discussion are missing. Since the authors used "Our experience" in the title, the readers would expect some methods and results. I am surprised that the Reviewer #07646418 did not notice this. The second issue: The title of this article promises too much. The authors refer in the title to the mediators of inflammation, while they studied only Mast cells, related proteins and refer to angiogenesis. Therefore, the title should be modified, *e.g.*, "Relationship between mediators of inflammation and pancreatic cancer: focus on mast cells and …. Our experience"; "Relationship between mast cell, angiogenesis and pancreatic cancer. Our experience"; or similar.

The article: "Understanding the molecular crossroads in acute liver failure: A pathway to new therapies[52]" has only Abstract, Introduction and Conclusion.

I like the following articles: (1) Title: "Role of gut-liver axis and glucagon-like peptide-1 receptor agonists in the treatment of metabolic dysfunction-associated fatty liver disease[53]". Excellent summary of pathophysiology and clinical relevance; and (2) Title: "Double contrast-enhanced ultrasonography improves diagnostic accuracy of T staging compared with multi-detector computed tomography in gastric cancer patients[54]" Clinically important topic.

***WJG*v30i24:** I reviewed the June 28, 2024 newest *WJG* issue. This issue contains 12 articles (including 6 editorials, 1 retrospective, 1 observational, 1 basic, 1 scientometric, and 2 letters to the editor). I found this issue well organized and interesting.

I like the following articles: (1) Title: "Mapping global research trends: Nutrition associations with nonalcoholic fatty liver disease - a Scopus bibliometric analysis[55]" While this article was not rated well by the reviewers, it is in my opinion, an important paper providing new views on this prevalent disease. It is my article of choice; and (2) Title: "Alanine aminotransferase predicts incident steatotic liver disease of metabolic etiology: Long life to the old biomarker![56]" Possibly "incident" should be changed to "incidence of". The paper provided a nice review of ALAT history in the diagnosis of liver diseases.

In the paper, "Fecal calprotectin and endoscopic scores: The cornerstones in clinical practice for evaluating mucosal healing in inflammatory bowel disease[57]". The subheading, "FECAL BIOMARKERS AND MUCOSA HEALING IN PATIENTS WITH IBD" "mucosa" should be changed to "MUCOSAL".

The reviewers did an overall good job.

CONCLUSION

After the first 6 months of the year 2024, as the Editor-in-Chief of *WJG*, I wish to share with readers the evolution of my process of carefully reviewing all published articles, including my considerations of the title, clinical and research importance, originality, novelty, and rating by the peer reviewers. I perform this service every week before a new issue's online publication. Based on this review process, I indicate my papers of choice and suggest changes to enhance them (*e.g.*, in the titles), sharing the comments with the company editors responsible for publication. This time- and effort-intensive process allows me to ensure the quality of publications and highlight essential articles that could spur readers to revisit an issue or delve deeper into papers that could benefit their own research or clinical activities or provide new knowledge in a seemingly unrelated topic that didn't first catch their attention.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Clinical features of gastroesophageal reflux disease and erosive esophagitis: Insights from patients undergoing esophagogastroduodenoscopy in resource-limited Ethiopia

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Abstract

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common disease worldwide with varying clinical presentations and risk factors. Prevalence data for Africa is lacking, but an increasing trend is expected due to demographic and epidemiological transitions. Although endoscopic studies for general gastrointestinal disorders have shown some patients with erosive esophagitis (EE), no studies in Ethiopia have investigated the clinical characteristics, risk factors, and severity of GERD using esophagogastroduodenoscopy (EGD).

AIM

To assess the clinical features of GERD in Ethiopian patients who underwent EGD and determine the severity and risk factors of EE.

METHODS

We conducted a multicenter, retrospective cross-sectional study of 221 patients diagnosed with GERD and endoscopic findings of EE at Trauma Associated Severe Hemorrhage and Amniotic Membrane Stem Cell between January 2019 and August 2022. Data were collected from electronic medical records and phone call interviews. We used descriptive statistics and binary logistic regression analysis with SPSS version 26 to identify the association between variables with a

statistical significance set at P value < 0.05.

RESULTS

The mean ± SD age of the patients was 44.8 (± 15.9) years, with a male-to-female ratio of 1.6:1. The most commonly reported symptom was epigastric pain (80.5%), followed by heartburn (43%). Los Angeles (LA)-A EE was diagnosed in 71.1% of patients, followed by LA-B (14.9%), LA-C (7.7%), and LA-D (5.9%). Multivariate analysis showed that age 50 or above, presence of bleeding, and endoscopic findings of duodenitis/duodenopathy were significantly associated with severe EE (P < 0.05). Stricture and Barrett's esophagus were observed in 4.5% and 1.36% of patients with EE, respectively.

CONCLUSION

Most of the patients had milder EE with fewer complications. However, severe EE was more prevalent in older patients and those with duodenitis/duodenopathy.

Key Words: Gastroesophageal reflux disease; Erosive esophagitis; Hiatal hernia; Esophagogastroduodenoscopy; Heart burn

Core Tip: This multicenter study in a resource-limited setting identified risk factors for severe erosive esophagitis (EE) in patients with gastroesophageal reflux disease (GERD) undergoing esophagogastroduodenoscopy. Age 50 years or above, bleeding, and duodenitis/duodenopathy were associated with worse EE. These findings can inform risk stratification for patients with GERD in similar settings.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a multifactorial process producing symptoms of heartburn and acid regurgitation, which occurs due to failure of the normal anti-reflux barrier[1-4]. It is diagnosed symptomatically by the occurrence of heartburn 2 or more days a week[5]. Most patients have no visible mucosal damage during endoscopy, whereas others have esophagitis, peptic strictures, or Barrett's esophagus (BE)[6-8]. The sensitivity of endoscopy for GERD is low, but it has high specificity at 90%-95%[9].

Accurate prevalence rates for GERD are difficult to ascertain with precision because many affected individuals, even those with BE, have no symptoms. Furthermore, data based on objective tests such as endoscopy and esophageal pH testing are impractical in extensive screening[10]. The pooled prevalence of at least weekly GERD symptoms reported from population-based studies worldwide is approximately 13%, but there is considerable geographic variation[11]. In 2009, there were 8.9 million outpatient clinic visits for GERD in the United States, which was the leading diagnosis for all gastrointestinal (GI) disorders[12].

No prevalence data from Africa are available, although it is believed to increase due to demographic and epidemiological transitions. The prevalence of GERD from endoscopic data of Ethiopian patients who underwent esophagogastroduodenoscopy (EGD) for dyspeptic symptoms was 2.3% in a study published in 2004[13] and 16.4% in a study done at St. Paul Hospital during 2013-2015[14].

There are several well-recognized risk factors for GERD and its complications[15]. There is no gender difference in Western society, but women are more symptomatic in the Middle East and South America[11]. Risk of erosive esophagitis (EE), BE, and adenocarcinoma is greater in men than in women[16]. Old age is strongly associated with complications of GERD[11]. In the United States, there is a similar prevalence of GERD symptoms among different races, but whites are at a greater risk for EE, BE, and adenocarcinoma of the esophagus[16].

The risk factors and the clinical profile of patients with GERD are variable and unknown in Africa. Furthermore, there is no data in Ethiopia from a study done in patients with GERD. Therefore, this study aims to assess the clinical features of GERD in Ethiopian patients who underwent EGD, determine the incidence and severity of EE in this population, and assess EE-related risk factors and comorbidities.

MATERIALS AND METHODS

Study design

A retrospective cross-sectional study was conducted in Tikur Anbesa specialized hospital (TASH) score and Adera medical and surgical center (AMSC) from August 2022 to October 2022, using the electronic medical records (EMR) registry, phone call interviews, and endoscopic Health Management Information Systems (HMIS) data registered between January 2019 and August 2022. All adult patients (> 18 years) who underwent EGD and were diagnosed with EE during the study period at both centers were included in the study. Patients with incomplete data, gastric outlet obstruction, gastric cancer, and esophageal cancer were excluded.

Study procedure

A structured questionnaire adopted and modified from different literature addressing similar objectives was prepared (Supplementary material). The questionnaire comprised three sections. The first focused on demographic information and risk factors for GERD, encompassing age, gender, residence, education, occupation, marital status, religion, comorbidities, body mass index (BMI), family history, lifestyle habits, medication use, and GERD-related factors. The second delved into disease characterization, such as symptoms, alarm signs, complications such as bleeding and ulcers, and laboratory results like complete blood count and *Helicobacter pylori* (*H. pylori*) stool test. The third was dedicated to endoscopic findings. Patient medical record numbers were taken from the endoscopic HMIS registry, and the EMR registry of each patient with EE was reviewed. After eligibility was checked, the data was registered. After briefly explaining the aim of the research and obtaining phone consent, phone call interviews were used to collect further data not found in the EMR registries.

Sampling procedures

All patients who were eligible during the study period were included. Given the descriptive nature of our study, we didn't calculate the sample size to include all corner samples of patients. Increasing the study's sample size gives more power to detect actual effects, provide more accurate and stable estimates, and generalize findings to a broader population during the regression analysis.

Statistical analysis

After verifying, completing, and checking data for quality, it was entered into SPSS version 26 and then analyzed. Results were summarized using tables and figures. Categorical variables were expressed as frequencies and percentages. Means, SD, and minimum and maximum values were used to express continuous variables. Independent variables were noncollinear after checking for multicollinearity using variance inflation factor (VIF). Univariate analysis was assessed using logistic regression for each independent variable with endoscopic severity of EE. Multivariate analysis was then assessed using binary logistic regression to determine the association of independent variables with the severity of EE. A *P* value less than 0.05 is considered statistically significant, and an odds ratio with a 95% confidence interval (95%CI) is used to determine the presence, strength, and direction of association between covariates and the dependent variable.

RESULTS

During the study period, 335 endoscopic records were reviewed (101 at TASH and 234 at AMSC). Among them, 221 (66%) met the inclusion criteria and were included in the analysis (Figure 1).

Sociodemographic profiles

The mean ± SD age of the participants was 44.8 ± 15.9 with a wide range (18-89 years). Most participants (37.6%) fell within the 30-44-year age range, whereas the least represented group was young adults aged 18-29 years (17.6%). Nearly a quarter of patients were between age group 45 and 59 years, and 19% of the participants were 60 years or older. The study was male predominant (62%), and most were married (70%). Almost all participants (95%) lived in urban areas, and a significant portion (72.4%) resided in Addis Ababa.

Risk factors of GERD

Nearly half of patients had a normal BMI (51.6%), whereas 75% fell within the overweight range (BMI 24.9-29.9). Only 8.6% of patients were obese (BMI > 30). Two patients reported worsening of symptoms and diagnosis during the time of pregnancy. One patient had a history of myotomy for achalasia. A family history of similar symptoms was reported by 17.6% of the patients. A total of 18 patients reported the use of traditional herbs recent or remote from their symptom onset. Eleven (5%) were current smokers, and eight (3.6%) had a previous smoking history. Moreover, 22.2% of patients reported occasional alcohol consumption, whereas 12.7% consumed more than one drink per week. The most common drug reported was calcium channel blocker, taken by patients with hypertension (HTN) and scleroderma. Aspirin or nonsteroidal anti-inflammatory drug (NSAID) use was reported in 5.9% of patients. Regarding the dietary pattern of patients, spicy food, the local spice Berbere, was the most commonly consumed item, followed by coffee, meat, and fatty foods (Figure 2). Table 1 summarizes the risk factors of GERD.

Table 1 Risk factors of patients with erosive esophagitis at Tikur Anbesa specialized hospital and Adera medical and surgical center during the study period

Risk factors		Number (*n*)	Percentage (%)
BMI	Less than 18.5	13/221	5.9
	18.5-24.9	114/221	51.6
	24.9-29.9	75/221	33.9
	30 and above	19/221	8.6
Risk factor history	Family history present	39/221	17.6
	Symptoms during pregnancy	2/84	2.4
	Traditional herb use	18/221	8.1
	Myotomy for Achalasia	1/221	0.5
Smoking	Current smoker	11/221	5%
	Ex-smoker	8/221	3.6
Alcohol	Occasional	49/221	22.2
	More than 1 drink/week	28/221	12.7
Drug history	CCB	27/221	12.2
	Aspirin/NSAID	13/221	5.9
	Prednisolone	4/221	1.8
	Metformin	4/221	1.8
	Iron	2/221	0.9

BMI: Body mass index; CCB: Calcium channel blocker; NSAID: Nonsteroidal anti-inflammatory drug.

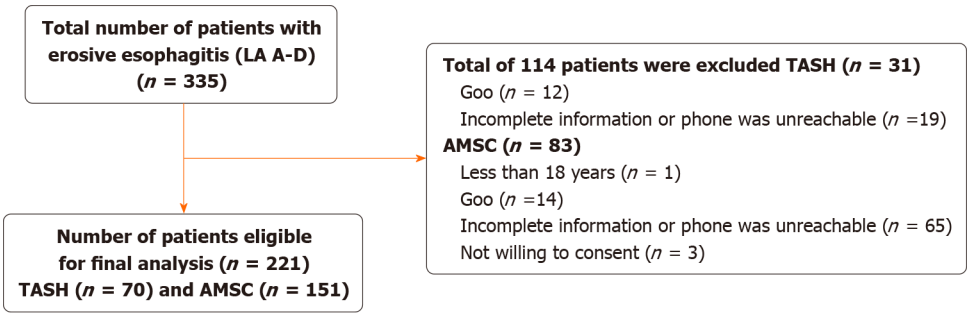

Figure 1 Patient selection flow chart. LA: Los Angeles; TASH: Tikur Anbesa specialized hospital; AMSC: Adera medical and surgical center; GOO: Gastric outlet obstruction.

Comorbidities of GERD

HTN was the most prevalent comorbidity, affecting 12% of the patients, followed by irritable bowel syndrome (IBS; 9%) and diabetes mellitus (DM; 6.8%). Among GERD-specific comorbidities, 15 patients (6.8%) had suspected or proven laryngopharyngeal reflux, 3 had scleroderma, and none had Zollinger-Ellison syndrome. Table 2 summarizes the comorbidities of patients with GERD.

Clinical characteristics

Typical reflux symptoms such as heartburn, regurgitation, and water brash were reported in less than half of the patients (45.7%). The most commonly reported symptom overall was epigastric burning pain (80.5%), followed by heartburn (43%) and intermittent or persistent vomiting in 28.9% of patients. Cough and pharyngeal pain were the most reported extraintestinal atypical symptoms, each accounting for 9%. Chest pain and globus were reported in 11 (5%) of patients each. Among the alarm features, 26.7% of patients reported mild to significant weight loss, 14.5% had hematemesis or melena, 7.2% had dysphagia, and 6.6% had anemia.

Twenty-three percent of patients reported long-standing symptoms lasting more than 2 years before undergoing endoscopy. Most (33.9%) had symptoms lasting between 6 months and 2 years. Of 221 patients, 155 tested for *H. pylori*

Table 2 Co-morbidities of patients with erosive esophagitis at Tikur Anbesa specialized hospital and Adera medical and surgical center during the study period

Co-morbidities	Number (*n*)	Percentage (%)
Diabetes mellitus	15/221	6.8
HTN	28/221	12.7
NAFLD	7/221	3.2
Dyslipidemia	13/221	5.9
CLD/PHTN	14/221	6.3
Asthma	4/221	1.8
IBS	20/221	9
Cholelithiasis	7/221	3.2
Scleroderma	3/221	1.4
Laryngopharyngeal Reflux	15/221	6.8

HTN: Hypertension; NAFLD: Nonalcoholic fatty liver disease; CLD: Chronic liver disease; PHTN: Portal hypertension; IBS: Irritable bowel syndrome.

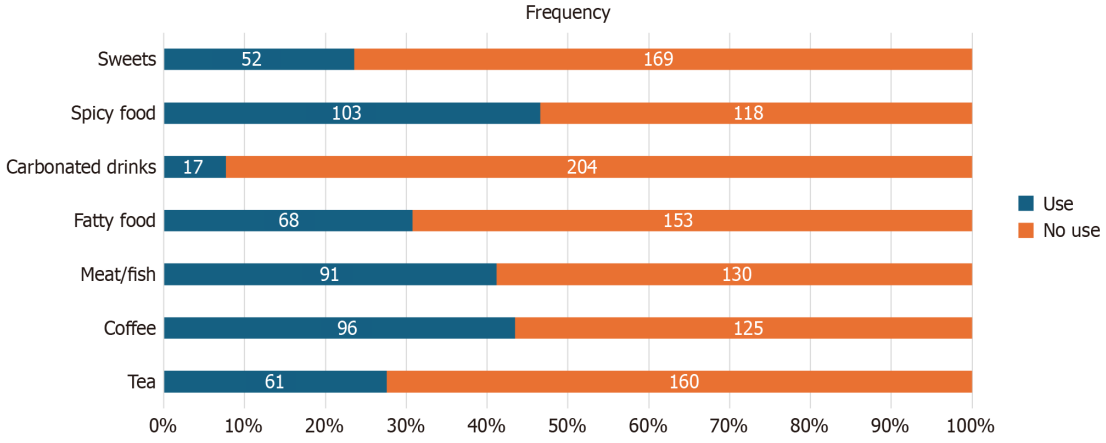

Figure 2 The dietary patterns of patients with erosive esophagitis at Tikur Anbesa specialized hospital and Adera medical and surgical center were reported during the study period.

using a stool antigen test. Of those tested, 121 (78%) received negative results. Table 3 and Figure 3 summarize the clinical characteristics of patients and the frequency of specific GERD symptoms, respectively.

Endoscopic characteristics

Dyspeptic symptoms not responding to proton pump inhibitors with or without alarm features were the most common indication for EGD (69.2%), followed by reflux symptoms (32.6). EGD was done without significant symptoms for another purpose (esophageal varices screening in eight patients) and found to have EE. Los Angeles (LA) used to grade EE. Most (71.5%) patients had LA-A, followed by LA-B (14.9%). The remaining had severe esophagitis: 7.7% LA-C and 5.9% LA-D. Moreover, 45.7% had hiatal hernia (HH). Barrett's appearing mucosa was seen in 3 out of 221 patients (one reported as a short segment, the second C1M2, and the third C3M2). Histologic confirmation was available for the patient with C1M2. There was no report of eosinophilic esophagitis. Concomitant gastric and duodenal ulcers were found in 4.1% and 11.3% of patients, respectively. Duodenopathy and gastropathy, visual diagnoses that are not histologically confirmed, were observed in 10% and 31.7% of patients, respectively. In addition, 5.9% of patients had bile acid gastropathy. Stricture, a complication of GERD, was identified in 4.5% of patients. Other complications were not reported (Table 4).

Factors associated with the severity of EE

Multicollinearity was checked using the VIF. Binary logistic regression was used to assess potential factors associated with severe EE (P value < 0.25), revealing 11 potential factors: Age over 50 years, presence DM, use of NSAIDs, absence of typical symptoms, presence of bleeding, a negative *H. pylori* stool antigen test, presence of bile reflux gastropathy, presence of a duodenal ulcer, presence of duodenopathy/duodenitis, absence of antral gastritis/gastropathy, and absence

Table 3 Clinical characteristics of patients with erosive esophagitis at Tikur Anbesa specialized hospital and Adera medical and surgical center during the study period

Clinical characteristics		Number (*n*)	Percentage (%)
Typical symptoms		101/221	45.7
Atypical intestinal symptoms		202/221	91.4
Atypical extra intestinal symptoms		50/221	22.6
Alarm features	Loss of appetite	35/221	15.8
	Weight loss	59/221	26.7
	Dysphagia	16/221	7.2
	Odynophagia	3/221	1.4
	Anemia	12/181	6.6
	UGIB	32/221	14.5
Duration of symptoms	Less than three months	43/221	19.5
	3-6months	52/221	23.5
	Six months to 2 years	75/221	33.9
	More than two years	51/221	23.1
Helicobacter pylori stool antigen	Not done	66/221	29.9
	Negative	121/221	54.8
	Positive	34/221	15.4

UGIB: Upper gastrointestinal bleeding.

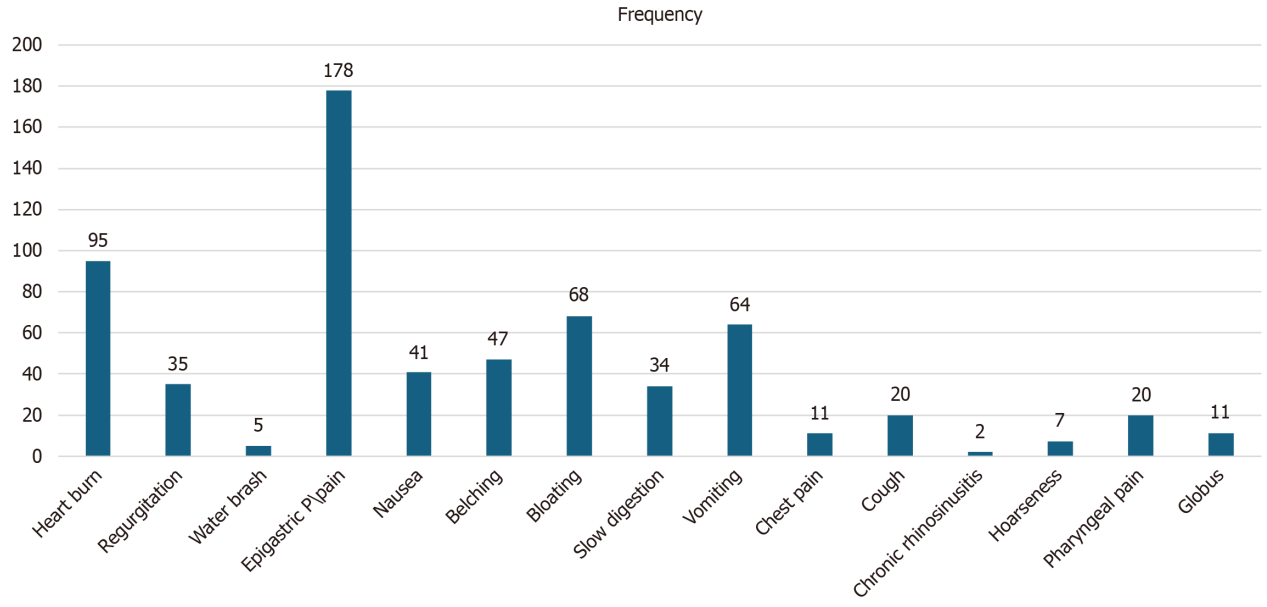

Figure 3 Specific symptoms reported by patients with erosive esophagitis at Tikur Anbesa specialized hospital and Adera medical and surgical center during the study period.

of pangastritis/gastritis. A multivariate logistic regression analysis was then conducted using all variables except the *H. pylori* test, which was excluded due to missing data. Only three variables had statistically significant associations with the severity of EE (P value < 0.05). Patients aged 50 years and above had a more than twofold increased risk of severe EE compared with younger patients. In addition, presentation with upper gastrointestinal bleeding (UGIB) increased the risk of severe esophagitis by 2.6 times. Finally, having duodenopathy as a comorbidity was associated with a 3.5-fold greater likelihood of severe EE grades (Table 5).

Table 4 Endoscopic characteristics of patients with erosive esophagitisat Tikur Anbesa specialized hospital and Adera medical and surgical center during the study period

Endoscopic findings		Frequency (*n*)	Percentage (%)
HH		101/221	45.7
Erosive esophagitis	LA-A	158/221	71.5
	LA-B	33/221	14.9
	LA-C	17/221	7.7
	LA-D	13/221	5.9
Barrett's esophagus		3/221	1.4
Gastric ulcer		9/221	4.1
Duodenal ulcer		25/221	11.3
Stricture		10/221	4.5
Gastropathy/gastritis		70/221	31.7
	Pan gastropathy	12/70	
	Antral gastropathy	58/70	
Bile reflux gastropathy		13/221	5.9
Duodenopathy/duodenitis		22/221	10
Others	Portal hypertensive gastropathy	4/221	1.8
	Grade 1 EV	3/221	1.4
	GAVE	1/221	0.5
	Gastric polyp	2/221	0.9

HH: Hiatal hernia; LA: Los Angeles; EV: Esophageal varices; GAVE: Gastric antral vascular ectasia.

DISCUSSION

This study aimed to assess the clinical features, complications, and risk factors for GERD and the severity of EE in Ethiopian patients. It was found that 71.5% had LA-A EE and a large proportion (91.4%) of patients presented with atypical symptoms. Age, the presence of UGIB, and the presence of duodenopathy/duodenitis were significantly associated with the severity of EE. The mean age of our patients (44.8 years) was similar to an Egyptian study[17] and younger than patients in the study from China (58.6 years)[18]. The male-to-female ratio was 1.6:1, consistent with most studies showing male predominance[17-19].

In our study, 45.7% of patients reported typical reflux symptoms such as heartburn, regurgitation, and water brash. Epigastric burning pain was the most prevalent symptom, affecting around 80.5% of patients. It suggests that patients might not consider typical reflux symptoms as significant indicators of GERD. This finding aligns with a Vietnamese study where epigastric pain and regurgitation were the most common complaints. In contrast to our study, only 9.2% of patients in the Vietnamese study reported that heartburn was their primary complaint. This difference could be due to the difficulty of expressing heartburn in most Asian languages[20]. A possible explanation for the predominance of epigastric burning pain in our study could be the high prevalence of overlapping diagnoses such as gastritis, duodenitis, or ulcer disease.

Consistent with prior studies, we found that older age (> 50 years) was significantly associated with the severity of EE [adjusted odds ratio (AOR): 2.331, 95%CI: 1.169-4.649, $P = 0.016$][11,21-23]. Similarly, UGIB was a significant risk factor for severe EE (AOR: 2.603, 95%CI: 1.111-6.098, $P = 0.028$). This finding aligns with a study from the United Kingdom[22]. However, UGIB can have other causes besides GERD. Our study found a high prevalence of overlapping diagnoses that can cause GI bleeding, such as duodenal ulcer and duodenitis/duodenopathy. These findings align with the Scottish study, which showed an overlapping duodenal ulcer and EE diagnosis[24]. However, only duodenitis/duodenopathy was associated with the severity of EE (AOR: 3.517 [1.259-9.824], $P = 0.016$). Bile acid reflux gastropathy (BRG) was found in 5.9% of our patients, but it was not related to severe EE. These findings contrast with the study in Greece, which showed an association between BRG and severe grades of esophagitis[25].

Several studies have reported a positive association between obesity and reflux esophagitis[15,18,20]. However, few have specifically investigated the link between obesity and the severity of esophageal inflammation. Our study did not find a significant association between BMI and EE severity. This finding aligns with the Loiano-Monghidoro study[26]. An American study demonstrated that LA-D patients had a lower BMI than LA-A patients[27]. However, El-Serag and Johanson[28] found that obesity was an independent risk factor for severe esophagitis. The lack of association in our

Table 5 Factors associated with the severity of erosive esophagitis in patients with erosive esophagitisat Tikur Anbesa specialized hospital and Adera medical and surgical center during the study period

Variables	Severity of EE					
	LA-A	LA-B/C/D	COR (95%CI)	*P* value	AOR (95%CI)	*P* value
Age of the study participants						
Less than 50	107	32	1			
50 and above	51	31	2.032 (1.12-3.689)	0.02	2.331 (1.169-4.649)	0.016[a]
Diabetes mellitus						
None	150	56	1			
Present	8	7	2.344 (0.812-6.764)	0.115	1.826 (0.455-7.330)	0.396
NSAID use						
None	152	56	1			
Present	6	7	3.167 (1.020-9.829)	0.046	1.681 (0.409-6.915)	0.472
Typical symptoms						
None	80	40	1.696 (0.93-3.091)	0.085	1.800 (0.909-3.563)	0.092
Present	78	23	1			
UGIB						
None	141	48	1			
Present	17	15	2.592 (1.203-5.585)	0.015	2.603 (1.111-6.098)	0.028[a]
Helicobacter pylori antigen						
Positive	29	5	1		-	-
Negative	88	33	2.175 (0.777-6.092)	0.139	-	-
Bile acid gastropathy						
None	151	57	1			
Present	7	6	2.271 (0.732-7.045)	0.156	1.812 (0.521-6.299)	0.350
Duodenal ulcer						
None	145	51	1			
Present	13	12	2.624 (1.125-6.122)	0.026	2.405 (0.918-6.301)	0.074
Duodenopathy/duodenitis						
None	147	52	1			
Present	11	11	2.827 (1.157-6.908)	0.023	3.517 (1.259-9.824)	0.016[a]
Antral gastritis/gastropathy						
None	111	52	2.002 (0.960-4.172)	0.064	2.229 (0.997-4.986)	0.051
Present	47	11	1			
Pan gastritis/gastropathy						
None	147	62	4.639 (0.586-36.712)	0.146	8.256 (0.967- 70.531)	0.054
Present	11	1	1			

[a]$P < 0.05$, and it is statistically significant.

EE: Erosive esophagitis; COR: Common odds ratio; AOR: Adjusted odds ratio; 95%CI: 95% confidence interval; LA: Los Angeles; NSAID: Nonsteroidal anti-inflammatory drug; UGIB: Upper gastrointestinal bleeding.

study might be due to its relatively small sample size and the predominance of patients with normal BMI and milder disease.

In our study, 12% of patients had HTN, 6.8% had type 2 DM, 3.2% had nonalcoholic fatty liver disease, and 5.9% had dyslipidemia. Although a Korean study showed an association between metabolic syndrome and the development and severity of EE[29] , our study did not find an association, possibly due to the smaller proportion of patients with DM, HTN, and dyslipidemia in our cohort. We observed a lower prevalence of concurrent IBS (9%) compared with the Nigerian study, which reported an overlap of GERD with dyspepsia and/or IBS in over 50% of cases[30].

Aspirin or NSAID use was reported in 5.9% of patients and was not associated with the severity of EE. The global GERD prevalence meta-analysis identified that aspirin was a risk factor[15], and one-third of patients in the Egyptian study reported NSAID use[17]. It is one of the predictors of EE[31].

H. pylori stool antigen testing was positive in 22% of tested patients. Univariate analysis suggested a link between *H. pylori* negativity and severe EE, aligning with Vietnamese and Iranian studies showing an increased risk in this population[20,32,33]. Due to incomplete *H. pylori* testing, we could not conduct a multivariate analysis to confirm the suggested negative association.

In contrast to our findings, many studies have reported that smoking was a risk factor for EE[17,20,28]. However, the low proportion of active smokers (5%) in our study limited our ability to detect associations with EE severity. Alcohol is associated with EE diagnosis, but only a few studies have explored its link with the severity of EE. Even an American study found an inverse relationship between the severity of EE and alcohol use[27]. In our study, 22.2% of patients reported occasional alcohol consumption, whereas 12.7% consumed more than one drink per week. Neither frequency of alcohol intake showed a significant association with the severity of EE.

Endoscopy revealed HH in 45.7% of our patients. The prevalence in our patient population was higher compared to a study comparing African American and non-Hispanic whites[34]. Contrary to some prior studies, we did not find an association between HH and the severity of EE[15,17,20,26]. Interestingly, HH was present in similar proportions across all EE severity groups in our study. Strictures occurred in ten patients (4.5%), which was lower than what is mentioned in the literature (7% to 23%)[35]. BE was identified in only 1.36% of our patients, consistent with the lower prevalence observed in Black populations[36]. The prevalence of BE is lowest in African American females compared to other race [37].

Strengths and weakness of the study

This study investigated a prevalent health issue in Ethiopia and aimed to generate new data that were not previously explored. To overcome the limitations of a retrospective design, phone interviews were conducted to gather additional information. Including multiple hospitals strengthens the generalizability of the findings within a hospital setting. Enrolling participants through EGD ensured a high degree of diagnostic accuracy for GERD.

However, the study is limited by a relatively small sample size, particularly in one group, and this could affect the detection of associations between factors and disease severity. In addition, missing data on *H. pylori* infection limited its inclusion in the analysis. As a hospital-based study, the generalizability to the entire population is restricted. Furthermore, the study only focused on a specific group of patients with GERD and the retrospective design limited control over confounding factors.

CONCLUSION

Our study of Ethiopian patients with GERD who underwent EGD provided population-specific insights into the clinical features of GERD, the association of GERD with EE, and risk factors for EE in patients with GERD. Notably, a large portion of these patients presented with atypical symptoms of GERD, most commonly burning epigastric pain. The mean age of Ethiopian patients with GERD and EE was 44.8 years, with a predominance of LA-A EE. However, over half of patients with EE did not report reflux symptoms as their primary complaint. Only older age, a history of UGIB, and duodenitis/duodenopathy had significant association with severe EE. The prevalence of complications associated with EE was lower in our patient population.

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FOOTNOTES

Author contributions: Mengistie FA and Ayalew ZS contribute equally to this study as co-corresponding authors. Mengistie FA and Shewaye AB contribute to the conceptualization, methodology, investigation, analysis, and writing of the manuscript; Tasamma AT and Ayalew ZS contribute to the methodology, data curation, drafting, interpretation, and edition of the data and supervision, supervision, and edition of the manuscript.

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ORIGINAL ARTICLE

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B-cell-specific signatures reveal novel immunophenotyping and therapeutic targets for hepatocellular carcinoma

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Abstract

BACKGROUND

Immunotherapy presents both promises and challenges in treating hepatocellular carcinoma (HCC) due to its complex immunological microenvironment. The role of B cells, a key part of the immune system, remains uncertain in HCC.

AIM

To identify B-cell-specific signatures and reveal novel immunophenotyping and therapeutic targets for HCC.

METHODS

Using the Tumor Immune Single-cell Hub 2 database, we identified B-cell-related genes (BRGs) in HCC. Gene enrichment analysis was performed to explore the possible collaboration between B cells and T cells in HCC. We conducted univariate Cox regression analysis using The Cancer Genome Atlas liver HCC collection dataset to find BRGs linked to HCC prognosis. Subsequently, least absolute shrinkage and selection operator regression was utilized to develop a prognostic model with 11 BRGs. The model was validated using the International Cancer

Genome Consortium dataset and GSE76427.

RESULTS

The risk score derived from the prognostic model emerged as an independent prognostic factor for HCC. Analysis of the immune microenvironment and cell infiltration revealed the immune status of various risk groups, supporting the cooperation of B and T cells in suppressing HCC. The BRGs model identified new molecular subtypes of HCC, each with distinct immune characteristics. Drug sensitivity analysis identified targeted drugs effective for each HCC subtype, enabling precision therapy and guiding clinical decisions.

CONCLUSION

We clarified the role of B cells in HCC and propose that the BRGs model offers promising targets for personalized immunotherapy.

Key Words: B cell; Hepatocellular carcinoma; Immune microenvironment; Immunotherapy; Molecular subtype

Core tip: We have established a reliable B-cell-related genes (BRGs) prognostic model and novel molecular subtypes in hepatocellular carcinoma (HCC). The BRGs model revealed the immune status and personalized treatment options of HCC molecular subtypes. B cells may play a role in tumor cytotoxicity by activating $CD4^+$ and $CD8^+$ T cells in HCC.

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INTRODUCTION

Primary liver cancer is the eighth most common cause of cancer-related mortality, ranking third among all cancer-related deaths[1]. Hepatocellular carcinoma (HCC) constitutes 80% of all primary liver cancer cases. In 2019, approximately 747000 cases of HCC were reported globally, marking a 70% increase since 1990, with 480000 deaths attributed to HCC [1]. Given the malignancy of HCC, compounded by its central location within the vascular system, early systemic dissemination and metastasis are common, resulting in high recurrence rates even with curative surgery and combined radiochemotherapy[1,2]. Immunotherapy, purportedly capable of activating T cells or rejuvenating immunosurveillance against cancer[3], is regarded as the most promising approach for curing HCC[4,5]. Several multikinase inhibitors and antivascular endothelial growth factor receptor 2 antibodies have gained approval for advanced HCC treatment[6]. Nonetheless, immunotherapy exhibits only a modest response rate of 15%–30% among HCC patients[7]. This could be attributed to the current research predominantly focusing on T cells, leaving our understanding of the overall tumor immune microenvironment in HCC limited, thereby lacking specificity in identifying immunotherapeutic targets tailored to individual HCC patients. Consequently, there is an urgent need to elucidate the roles of other crucial immune cells such as B cells in HCC, facilitating improved immune stratification of patients for precision therapy, thus elevating the cure rate of HCC.

Currently, immunotherapy for tumors predominantly focuses on T-cell-mediated adaptive immunity. While B cells consistently represent a rich cellular component within tumors, little is known about their activation status and biological functions in human tumors, thus leading to a significant oversight of B cells in tumor immunotherapy[8]. Traditionally associated with humoral immune responses against viral and bacterial infections, the role of B cells in tumor immunity has long been debated and may exhibit cancer-specific characteristics[9]. The role of B cells in HCC remains obscure, yet mounting evidence from both preclinical and clinical studies suggests that B cells can induce potent anticancer immunity through humoral and cellular immune responses[8]; a hypothesis awaiting formal validation through analysis of HCC molecular features. B cells infiltrating tumors can be identified at various stages of HCC development, with their presence varying according to stage and histological subtype[10]. Given their influence on both humoral and cellular immunity, a deeper understanding of B-cell biology can offer significant opportunities for HCC immunotherapy[11]. Therefore, a thorough analysis of the specific role of B cells in HCC, along with their interplay with other crucial immune cells in HCC, is crucial for reshaping the immune landscape of the tumor microenvironment and treating HCC effectively.

In this study, we identified differentially expressed B-cell-related genes (BRGs) in HCC using the Tumor Immune Single-Cell Hub 2 (TISCH2) database. Gene enrichment analysis suggested potential synergy between B cells and T cells in HCC. Subsequently, using The Cancer Genome Atlas Liver Hepatocellular Carcinoma Collection (TCGA-LIHC) dataset, we conducted single-factor Cox regression analysis to screen BRGs associated with HCC prognosis. We used least absolute shrinkage and selection operator (LASSO) regression analysis to construct a prognostic evaluation model composed of 11 BRGs. The risk score derived from the BRG prognostic model was validated as an independent

prognostic factor for HCC, confirmed by the International Cancer Genome Consortium (ICGC) dataset and GSE76427. Extensive clinical correlation analysis demonstrated the association between the prognostic model and clinicopathological factors. Immune microenvironment and immune cell infiltration analyses revealed the immune status of different risk score groups, supporting the notion of B cells and T cells synergistically inhibiting HCC. Finally, through the BRGs model, we characterized three novel molecular subtypes of HCC, delineating their immune characteristics and identifying targeted drugs effective for each subtype, thus facilitating precision therapy for HCC and aiding clinical decision-making.

MATERIALS AND METHODS

Selection of differentially expressed BRGs in HCC

We downloaded single-cell RNA data of HCC, comprising 62 530 cells, from the Gene Expression Omnibus website GSE140228 dataset. We analyzed the single-cell data using the Transcriptomic-Immunohistochemical Single-Cell Hybridization (TISH2) website[12]. We used principal component analysis (PCA) for dimensionality reduction, K-nearest neighbors, and Louvain algorithms for cluster identification, and annotated cell types using marker genes[13,14]. By applying the Wilcoxon test, we identified differentially expressed genes in B-cell clusters compared to all other cells based on the logarithmic fold change (|fold change| ≥ 1.5) and false discovery rate (FDR) < 0.05[15].

Cell–cell communication analysis

We conducted Cell Chat analysis[16] using the TISH2 website[12] to assess cell–cell communication based on the expression of known ligand–receptor (L–R) pairs across different clusters. We utilized the netVisual_circle function from the pheatmap R package and the CellChat R package to compute and display the quantity of significant L–R interaction pairs and the communication probability between two clusters. Significant L–R interaction pairs were identified for each cluster, designating them as either source or target cells, with a *P* value threshold set at 0.05[12].

Functional enrichment analysis of different cell clusters

To characterize the functionality of distinct cell type populations, we conducted gene set enrichment analysis (GSEA) using the TISH2 website, ranking genes based on fold changes derived from differential analysis[12]. We used the Kyoto Encyclopedia of Genes and Genomes (KEGG), Gene Ontology (GO), and GSEA analyses to identify and visualize significantly upregulated and downregulated pathways within each cell cluster (FDR ≤ 0.05), facilitating functional enrichment analysis across different clusters[12].

Collection of HCC transcriptomic and clinicopathological data

We obtained transcriptomic data from the TCGA-LIHC dataset, comprising 375 HCC samples and 50 paired adjacent normal tissues. Among these, 365 patients had complete survival data, clinicopathological information, and somatic mutation data. Additionally, we collected transcriptomic and survival data from 232 HCC patients from the ICGC database. Transcriptomic and survival data from 115 HCC patients were retrieved from the GSE76427 dataset.

Construction and validation of prognosis-related BRGs model in HCC

Using the TCGA-LIHC database as the training set, we conducted univariate Cox regression analysis (FDR < 0.05) to identify BRGs associated with HCC prognosis. LASSO regression analysis was performed using the R glm Sparse Net package[17] to mitigate model overfitting, resulting in the derivation of an HCC prognosis model composed of 11 BRGs. The BRGs incorporated into the prognosis model and their corresponding gene coefficients are presented in Supplementary Table 1. Subsequently, we computed the risk scores for each HCC sample in TCGA-LIHC. Based on a 1:1 cutoff value, TCGA-LIHC samples were split into low- and high-risk groups. We used Kaplan–Meier survival and receiver operating characteristic (ROC)[17] analysis in R survival and R time ROC to evaluate the predictive accuracy of the model for HCC prognosis. The reliability of the BRGs model was validated using the ICGC dataset and GSE76427 as validation datasets.

Functional enrichment analysis of different risk score groups

Differential gene analysis between high-risk and low-risk groups in TCGA-LIHC was conducted using the limma package in R (|log fold change| > 1, FDR < 0.05). We used cluster Profiler[17] in R for KEGG and GO analysis to explore molecular mechanisms among HCC risk score groups. GSEA assessed biological functional changes between low- and high-risk subgroups (|normalized enrichment score| > 1, FDR < 0.05).

Assessing the clinical relevance of BRGs model

To demonstrate that the risk score was an independent prognostic factor for HCC, we conducted univariate Cox regression analysis (FDR < 0.05) and multivariate Cox regression analysis (FDR < 0.05) between the risk score and other clinicopathological factors of HCC using the survival package in R. We utilized the survminer[17] and time ROC[17] packages in R to generate ROC curves, illustrating the comparative efficacy of the risk score and other clinicopathological factors for HCC prognosis. Visualization of the correlation between the risk score and other clinicopathological factors of HCC was achieved using the Complex Heatmap and reshape2 packages in R.

Evaluation of the ability of the BRGs model to characterize the immune microenvironment of HCC

Various algorithms, including tumor immune estimation resource, single-sample GSEA (ssGSEA), microenvironment cell population counter, QUANTitative immune single-cell expression, estimation, cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT), and evaluating the proportion of immune cells[18], were used to calculate the relative levels of tumor-infiltrating immune cells in TCGA-LIHC samples. ssGSEA and CIBERSORT algorithms were utilized to compute the abundance of cell subpopulations in TCGA-LIHC samples. The ssGSEA algorithm was applied to assess the immune functional status in TCGA-LIHC samples.

Assessment of response to immunotherapy

We used the R packages limma and reshape 2[18] to identify differential expression of immune checkpoint genes across various risk score groups. Elevated expression levels of these genes may correlate with improved efficacy of immune checkpoint inhibitors. For the evaluation of immunotherapy effectiveness, a prognostic model based on Biomarker Response to Immunotherapy Group was applied to 348 malignant tumor patients undergoing immunotherapy within the IMvigor210 dataset.

Identification of novel molecular subtypes of HCC

The R package consensus cluster plus[18] was used for unsupervised consensus clustering to identify novel molecular subtypes of HCC. This package generated several key outputs: the consensus matrix (CM), cumulative distribution function (CDF) plot, and consensus heatmap were essential tools for identifying the ideal number of clusters for classifying HCC subtypes. The CDF plot provided a glimpse into the stability of clustering outcomes across various cluster numbers. The CM, displayed as a matrix, indicated the frequency with which sample pairs were grouped together across iterations, providing a quantitative measure of clustering robustness. The consensus heatmap visually represented the CM, facilitating a clearer interpretation of the clustering results.

Statistical analysis

All statistical analyses were performed using R version 4.3.1. The Kruskal–Wallis test was utilized to examine variances in immune scores, immune checkpoint gene expression, and drug sensitivity across different clusters. To compare the differences in patient survival rates between two risk groups, a log-rank test from the R survival package was used for Kaplan–Meier analysis. The statistical tests were two-sided, where $P < 0.05$ was considered significant. Statistical significance levels are denoted with asterisks: $^{a}P < 0.05$, $^{b}P < 0.01$, and $^{c}P < 0.001$.

RESULTS

B-cell-related immune microenvironmental crosstalk in HCC

The entire study followed the screening and analysis process outlined in Figure 1. We analyzed scRNA data from GSE140228 using TISCH2, and Figure 2A clearly shows the distinct segregation of B-cell subgroups. Both the pie chart and bar graph depict the number and proportion of B cells, demonstrating that they fell within the normal range (Figure 2B and C). In the tumor microenvironment, cellular interactions regulated cell function and influenced the surrounding immune environment and tumor progression. By using the cell chat algorithm in TISCH2, we predicted interactions between different cell types. The analysis showed strong interactions among B cells, most T cells, macrophages, and dendritic cells (Figure 2D and E), suggesting that B cells play a key role in the crosstalk within the HCC immune microenvironment. We examined the gene pairs involved in the interactions of B cells as donors (Figure 2F) or recipients (Figure 2G) with other cells. This revealed the probability of interactions among specific gene pairs, demonstrating that B cells significantly regulate various crucial genes of CD8 T cells such as *CD8A* and *CD8D*. To identify BRGs compared with genes of other cells, we utilized Wilcoxon tests available in TISCH2. We applied a log transformation fold change ($|\text{fold change}| \geq 1.5$) and FDR < 0.05 to recognize BRGs. The analysis identified 74 upregulated and 171 downregulated BRGs.

Functional characteristics of B cells in HCC

Various transcription factors play critical roles in the development and progression of HCC. We used the local indicators of spatial association algorithm within TISCH2 to infer the transcription factors regulating gene expression in each cell cluster. Using heatmaps, we demonstrated the expression patterns of key transcription factors across all cell clusters in the dataset. The expression patterns of transcription factors in B cells and T cells were almost identical (Figure 3A), supporting the potential synergistic immune role of B cells and T cells in HCC. Subsequently, we sought to identify cell-type-specific transcription factors. In B cells, transcription factors such as myelocytomatosis proto-oncogene, signal transducer and activator of transcription 5B, plant homeodomain finger protein 8, core-binding factor subunit, and E26 transformation-specific-related genes, *NRF1*, *FLI1*, *EGR3*, *TFAP4*, and *RUNX1* showed specific expression (Figure 3B). This specificity highlighted the unique regulatory mechanisms at play within B cells in the HCC immune environment.

To elucidate the specific functions that B cells may regulate in HCC and their synergistic interaction with T cells, we utilized TISCH2 GSEA along with a collection of 16 626 gene sets from the molecular signatures database to characterize the unique functions of B cells. These gene sets encompassed various domains including KEGG pathways, hallmark gene sets, GO terms, immunological features, oncogenic signatures, and transcription factor targets. We observed a strong correlation between B cells and multiple T-cell-related immunological gene sets (Figure 3C and D). In terms of KEGG

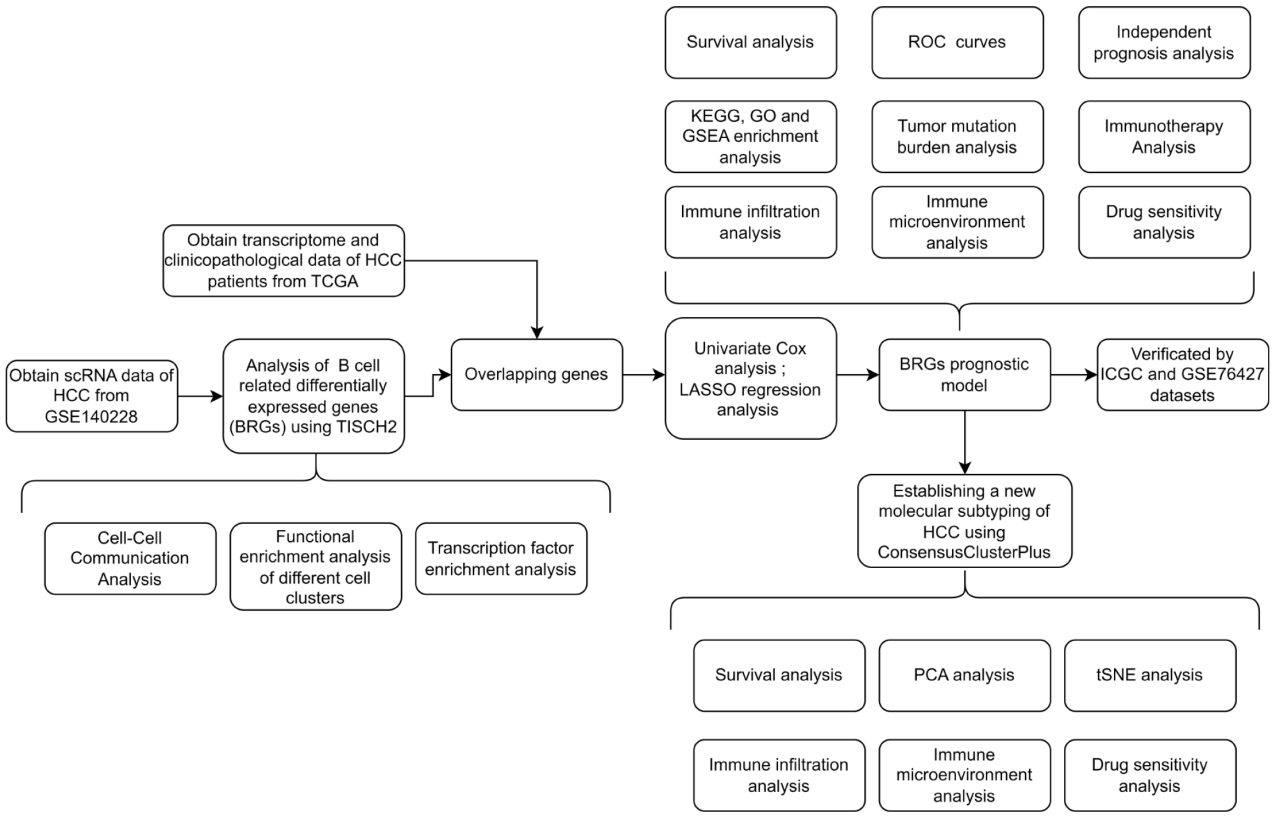


Figure 1 Detailed flowchart illustrates the identification and validation of the prognostic model associated with B-cell-related genes. HCC: Hepatocellular carcinoma; TCGA: The Cancer Genome Atlas; BRGs: B-cell-related genes; TISCH2: Tumor Immune Single-Cell Hub 2; ROC: Receiver operating characteristic; KEGG: Kyoto Encyclopedia of Genes and Genomes; GO: Gene Ontology; GSEA: Gene set enrichment analysis; LASSO: Least absolute shrinkage and selection operator; ICGC: International Cancer Genome Consortium; PCA: Principal component analysis; tSNE: T-distributed stochastic neighbor embedding; GSE: Gene Expression Omnibus Series.

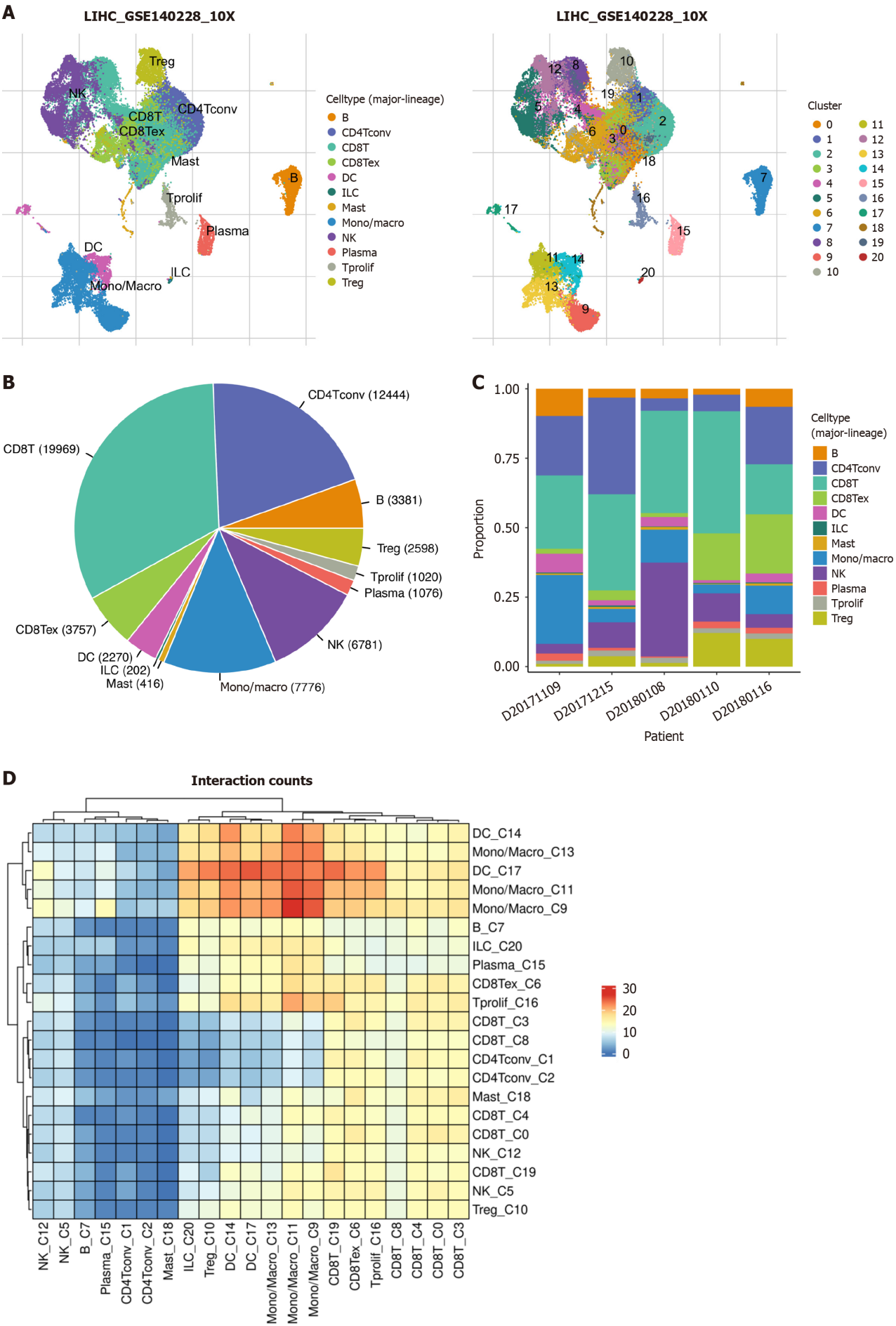
enrichment analysis, B cells and T cells exhibited highly consistent regulation of pathways such as T-cell receptor signaling, natural-killer-cell-mediated cytotoxicity, NOD-like receptor signaling, Toll-like receptor signaling, and ribosome pathways (Figure 3E and F). Regarding GO analysis, both B cells and T cells showed significant enrichment in pathways including nuclear transcribed mRNA catabolic processes involved in nonsense-mediated decay, translational elongation, RNA catabolic processes, presynaptic membranes, and cytosolic ribosomes (Figure 3G–L). These findings collectively suggest that B cells and T cells jointly regulate mRNA metabolism, mRNA translation, and subsequent immune responses in HCC.

Construction of BRGs prognostic model of HCC

Based on the BRGs selected from Figure 1H, we extracted the expression levels of these BRGs from the TCGA-LIHC database, and merged them with clinical, pathological, and prognostic data, resulting in an integrated table containing complete information for 365 patients. Through single-factor Cox regression analysis, we identified 41 BRGs associated with prognosis of HCC patients (Figure 4A), displaying their expression levels in HCC compared to paired adjacent cancer samples (Figure 4B). We used LASSO regression analysis to mitigate model overfitting, and derived an HCC prognostic model composed of 11 BRGs (Figure 4C and D, Supplementary Table 1). Utilizing Kaplan–Meier survival estimates, we evaluated the relationship between these BRGs and HCC prognosis, revealing that high expression levels of *BLNK*, *FYN*, and *KLRB1* were associated with favorable prognosis, whereas elevated expression of *CALM1*, *LEPROTL1*, *S100A10*, *MARCKSL1*, *LDHA*, *LYAR*, *CKLF*, and *TXN* correlated with poor prognosis (Figure 4E). Additionally, we presented the expression of these BRGs in B cells of HCC, noting high expression of *BLNK* and *MARCKSL1* in B cells, while *FYN*, *KLRB1*, *CALM1*, *LEPROTL1*, *S100A10*, *LDHA*, *LYAR*, *CKLF*, and *TXN* exhibited low expression (Figure 4F).

Validation of BRGs prognostic model for HCC

To evaluate the prognostic model of BRGs, we utilized TCGA-LIHC data as the training set, with ICGC and GSE76427 serving as validation sets. The expression patterns of the 11 BRGs in the prognostic model were consistent between the training and validation sets (Figure 5A–C). The distribution of HCC patients across different risk score groups (Figure 5D–F) and their survival status (Figure 5G–I) were largely consistent across various risk score groups. We depicted the prognostic performance of patients in different risk score groups within the training and validation sets. Consistently, patients in the high-risk score group exhibited poorer prognosis compared with those in the low-risk score group (Figure 5J–L). We constructed ROC curves to validate the effectiveness of the model. The area under the ROC curve (AUC) for 1, 2, and 3 years in the TCGA-LIHC dataset was 0.758, 0.768, and 0.787 respectively (Figure 5M); 0.787,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Mast
B
Tprolif
Plasma
DC
ILC
Mono/Macro
Celltype (major-lineage)
B
CD4Tconv
CD8T
CD8Tex
DC
ILC
Mast
Mono/macro
NK
Plasma
Tprolif
Treg
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CD8T (19969)
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DC (2270)
ILC (202)
Mast (416)
Mono/macro (7776)
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D20180108
D20180110
D20180116
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DC_C17
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Mono/Macro_C9
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ILC_C20
Plasma_C15
CD8Tex_C6
Tprolif_C16
CD8T_C3
CD8T_C8
CD4Tconv_C1
CD4Tconv_C2
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20
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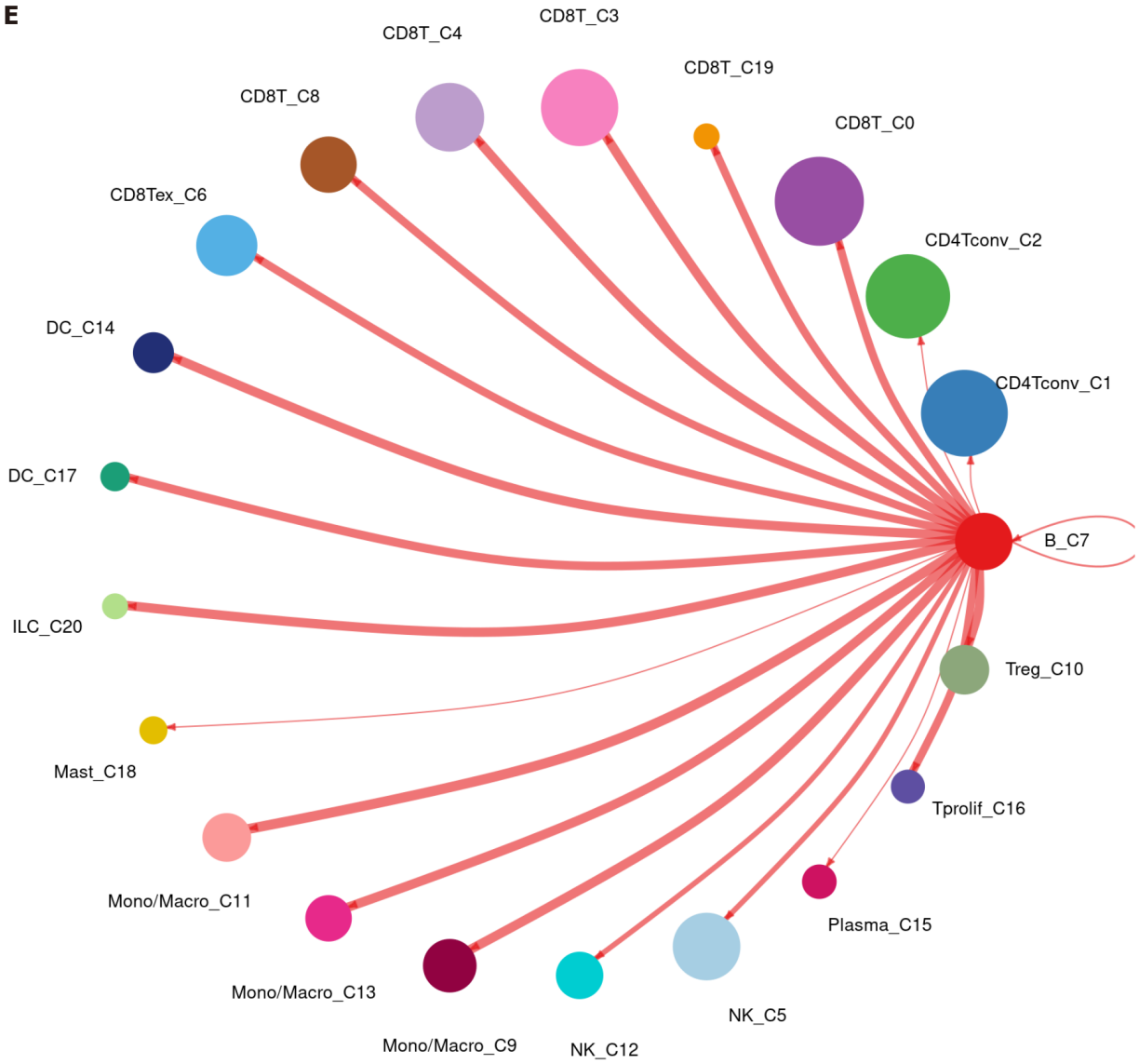
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ILC_C20
Treg_C10
Mast_C18
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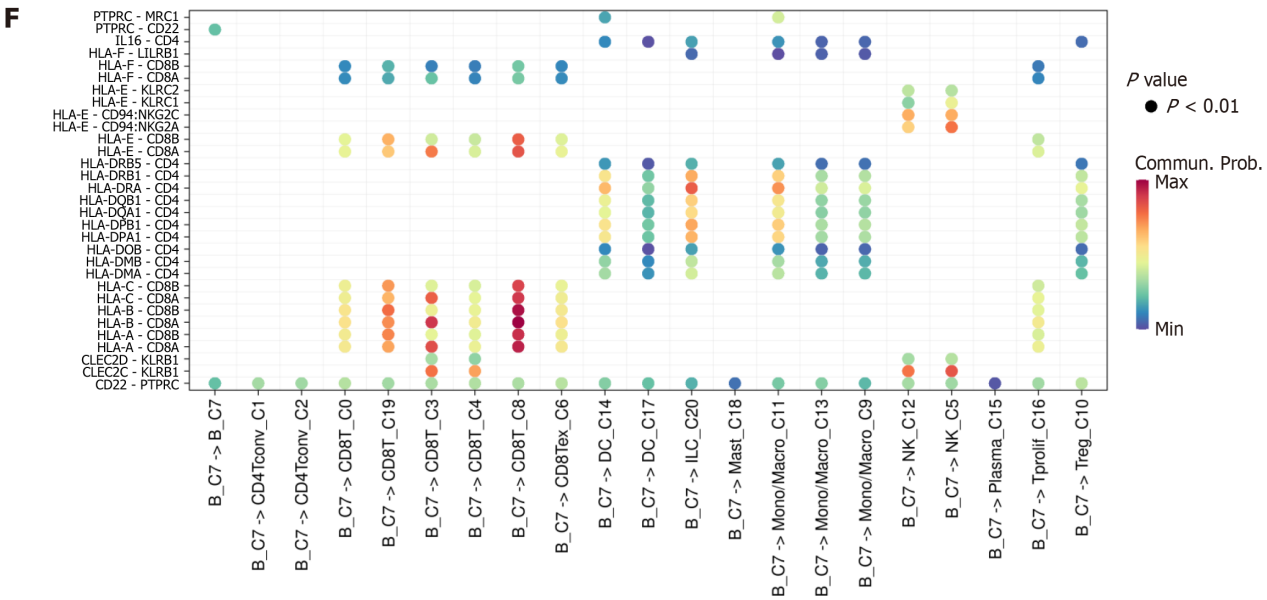
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PTPRC - CD22
IL16 - CD4
HLA-F - LILRB1
HLA-F - CD8B
HLA-F - CD8A
HLA-E - KLRC2
HLA-E - KLRC1
HLA-E - CD94:NKG2C
HLA-E - CD94:NKG2A
HLA-E - CD8B
HLA-E - CD8A
HLA-DRB5 - CD4
HLA-DRB1 - CD4
HLA-DRA - CD4
HLA-DQB1 - CD4
HLA-DQA1 - CD4
HLA-DPB1 - CD4
HLA-DPA1 - CD4
HLA-DOB - CD4
HLA-DMB - CD4
HLA-DMA - CD4
HLA-C - CD8B
HLA-C - CD8A
HLA-B - CD8B
HLA-B - CD8A
HLA-A - CD8B
HLA-A - CD8A
CLEC2D - KLRB1
CLEC2C - KLRB1
CD22 - PTPRC
B_C7 -> B_C7
B_C7 -> CD4Tconv_C1
B_C7 -> CD4Tconv_C2
B_C7 -> CD8T_C0
B_C7 -> CD8T_C19
B_C7 -> CD8T_C3
B_C7 -> CD8T_C4
B_C7 -> CD8T_C8
B_C7 -> CD8Tex_C6
B_C7 -> DC_C14
B_C7 -> DC_C17
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B_C7 -> Mast_C18
B_C7 -> Mono/Macro_C11
B_C7 -> Mono/Macro_C13
B_C7 -> Mono/Macro_C9
B_C7 -> NK_C12
B_C7 -> NK_C5
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Commun. Prob.
Max
Min

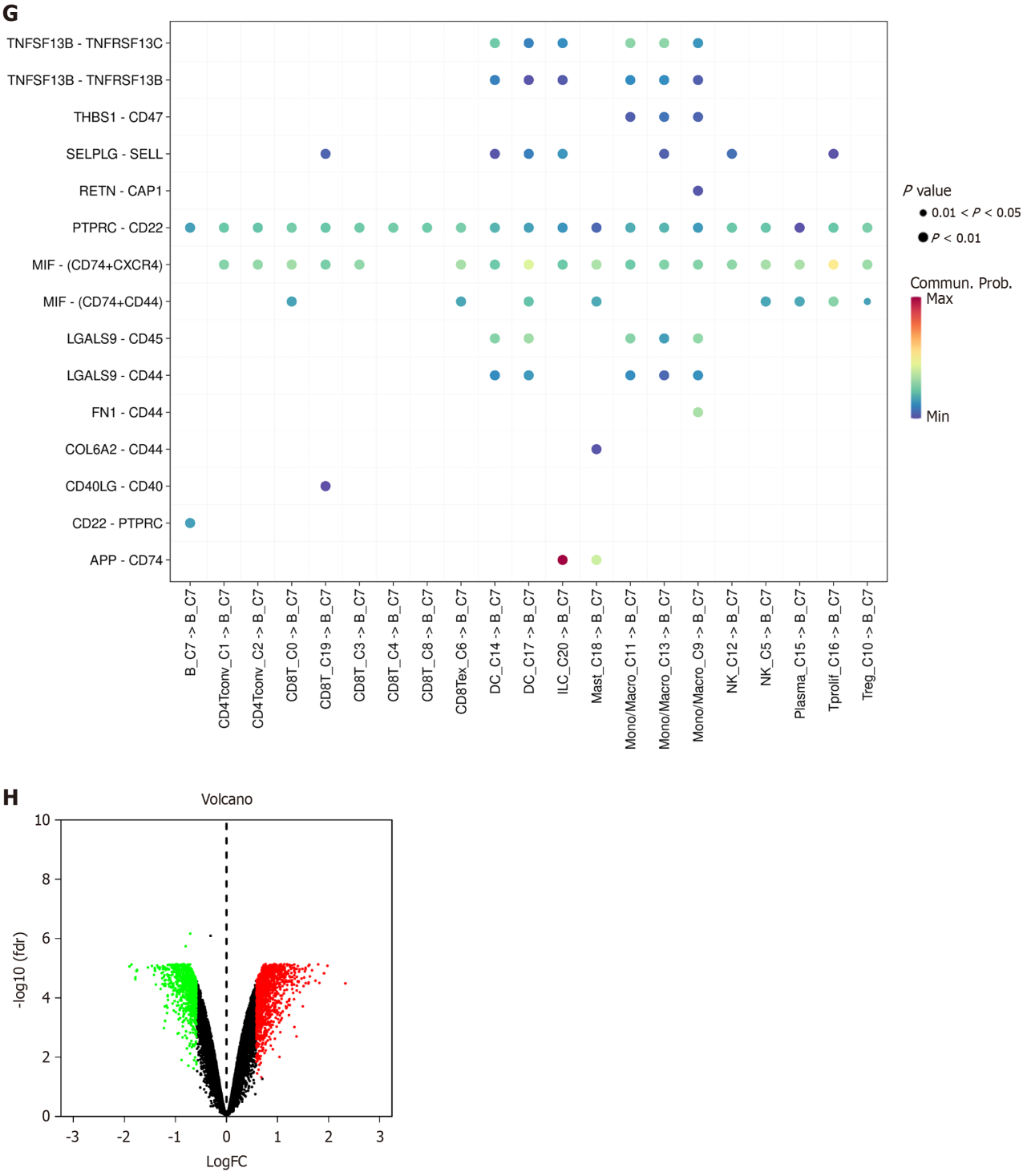
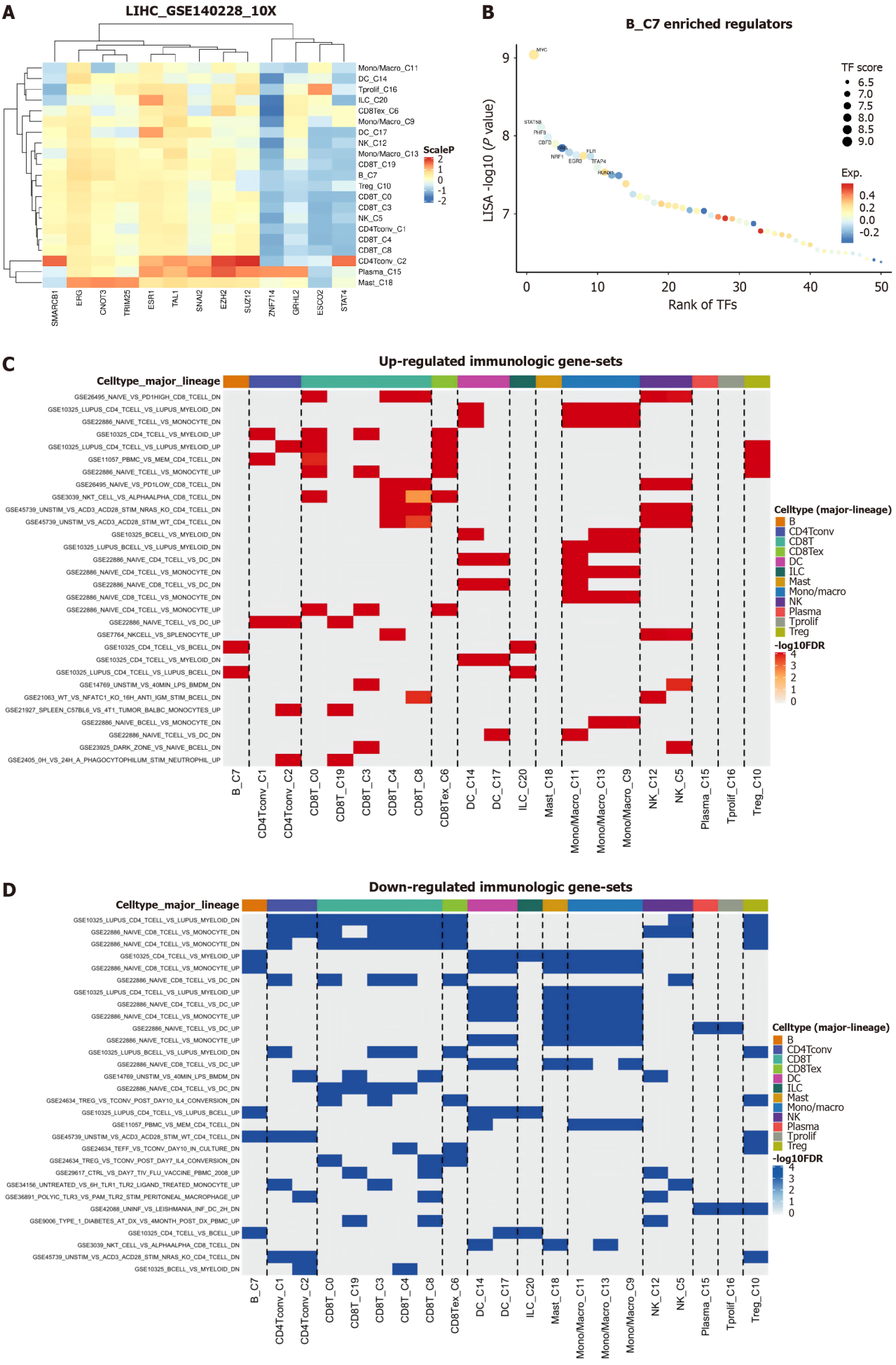


Figure 2 Cell-to-cell communication in hepatocellular carcinoma. A: Cellular map illustrates the distribution and abundance of various cell subgroups within hepatocellular carcinoma (HCC); B: Pie chart displays the accurate cell counts of each cell subgroup in HCC; C: Bar graph demonstrates the proportional distribution of each cell subgroup among individual HCC patients; D: Heatmap exhibits the number of gene pairs interacting between cell groups; E: Using cell chat, the interaction probability between specific cell groups and other cell groups is depicted; F: Using cell chat, the interaction probability is delineated between B cells as donors and specific gene pairs of other cells; G: Using cell chat, the interaction probability is delineated between B cells as recipients and specific gene pairs of other cells; H: Volcano plot showcases the differentially expressed genes within B cells. Red indicates fold change > 1.5 and FDR < 0.05; green indicates fold change < 1.5 and FDR < 0.05. LIHC: Liver hepatocellular carcinoma; NK: Nature kill; DC: Dendritic cells; HLA: Human leukocyte antigen.

0.707, and 0.701 in the ICGC database (Figure 5N); and 0.599, 0.655, and 0.637 in GSE76427 (Figure 5O). These results collectively affirm the efficacy of our BRG prognostic model in predicting the prognosis of HCC patients.

Clinical correlation analysis of BRGs prognostic model for HCC

To assess the guiding value of the BRGs prognostic model in clinical practice, we conducted Cox regression analysis to compare its predictive superiority regarding HCC patient prognosis with other clinicopathological factors. Single-factor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NK_C12
Mono/Macro_C13
CD8T_C19
B_C7
Treg_C10
CD8T_C0
CD8T_C3
NK_C5
CD4Tconv_C1
CD8T_C4
CD8T_C8
CD4Tconv_C2
Plasma_C15
Mast_C18
ScaleP
SMARCB1
ERG
CNOT3
TRIM25
ESR1
TAL1
SNAI2
EZH2
SUZ12
ZNF714
GRHL2
ESCO2
STAT4
B
B_C7 enriched regulators
LISA -log10 (P value)
Rank of TFs
TF score
Exp.
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RUNX1
C
Up-regulated immunologic gene-sets
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GSE45739_UNSTIM_VS_ACD3_ACD28_STIM_WT_CD4_TCELL_DN
GSE10325_BCELL_VS_MYELOID_DN
GSE10325_LUPUS_BCELL_VS_LUPUS_MYELOID_DN
GSE22886_NAIVE_CD4_TCELL_VS_DC_DN
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CD4Tconv_C2
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DC_C14
DC_C17
ILC_C20
Mast_C18
Mono/Macro_C11
Mono/Macro_C13
Mono/Macro_C9
NK_C12
NK_C5
Plasma_C15
Tprolif_C16
Treg_C10
Celltype (major-lineage)
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CD4Tconv
CD8T
CD8Tex
DC
ILC
Mast
Mono/macro
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Plasma
Tprolif
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Down-regulated immunologic gene-sets
Celltype_major_lineage
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CD4Tconv_C2
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ILC_C20
Mast_C18
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Tprolif
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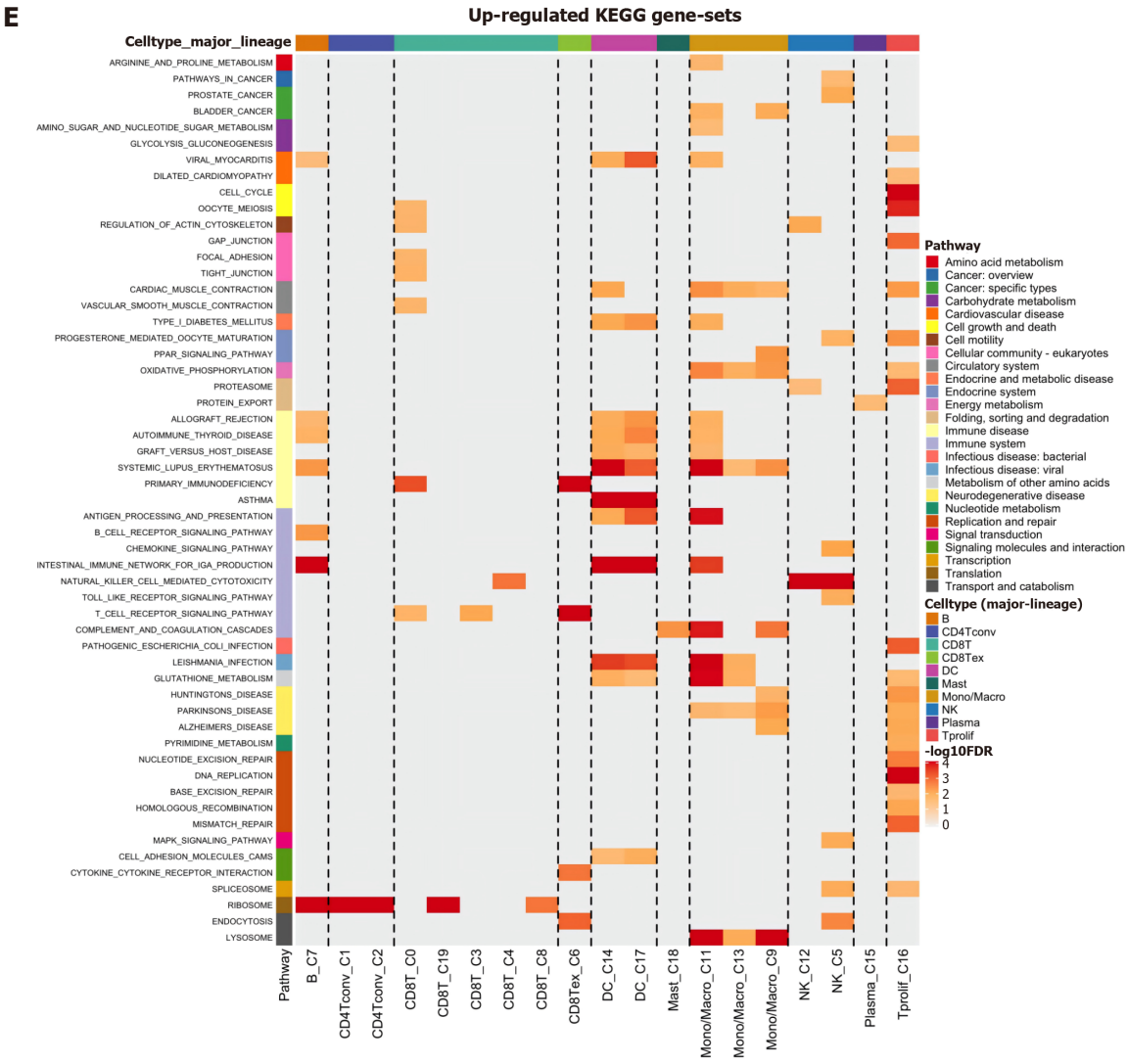
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GLYCOLYSIS_GLUCONEOGENESIS
VIRAL_MYOCARDITIS
DILATED_CARDIOMYOPATHY
CELL_CYCLE
OOCYTE_MEIOSIS
REGULATION_OF_ACTIN_CYTOSKELETON
GAP_JUNCTION
FOCAL_ADHESION
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CARDIAC_MUSCLE_CONTRACTION
VASCULAR_SMOOTH_MUSCLE_CONTRACTION
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PPAR_SIGNALING_PATHWAY
OXIDATIVE_PHOSPHORYLATION
PROTEASOME
PROTEIN_EXPORT
ALLOGRAFT_REJECTION
AUTOIMMUNE_THYROID_DISEASE
GRAFT_VERSUS_HOST_DISEASE
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DNA_REPLICATION
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HOMOLOGOUS_RECOMBINATION
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MAPK_SIGNALING_PATHWAY
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CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION
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ENDOCYTOSIS
LYSOSOME
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DC_C14
DC_C17
Mast_C18
Mono/Macro_C11
Mono/Macro_C13
Mono/Macro_C9
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NK_C5
Plasma_C15
Tprolif_C16
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Cancer: specific types
Carbohydrate metabolism
Cardiovascular disease
Cell growth and death
Cell motility
Cellular community - eukaryotes
Circulatory system
Endocrine and metabolic disease
Endocrine system
Energy metabolism
Folding, sorting and degradation
Immune disease
Immune system
Infectious disease: bacterial
Infectious disease: viral
Metabolism of other amino acids
Neurodegenerative disease
Nucleotide metabolism
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Signal transduction
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Transcription
Translation
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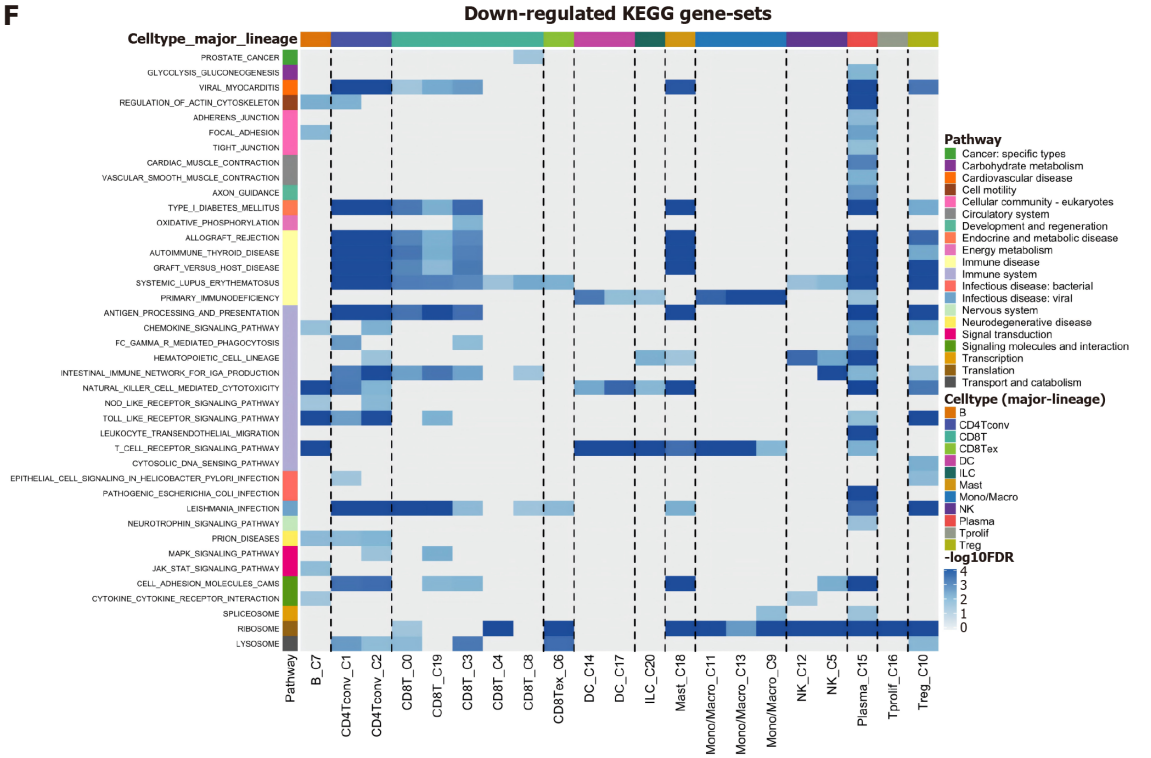
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ADHERENS_JUNCTION
FOCAL_ADHESION
TIGHT_JUNCTION
CARDIAC_MUSCLE_CONTRACTION
VASCULAR_SMOOTH_MUSCLE_CONTRACTION
AXON_GUIDANCE
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OXIDATIVE_PHOSPHORYLATION
ALLOGRAFT_REJECTION
AUTOIMMUNE_THYROID_DISEASE
GRAFT_VERSUS_HOST_DISEASE
SYSTEMIC_LUPUS_ERYTHEMATOSUS
PRIMARY_IMMUNODEFICIENCY
ANTIGEN_PROCESSING_AND_PRESENTATION
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NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY
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TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
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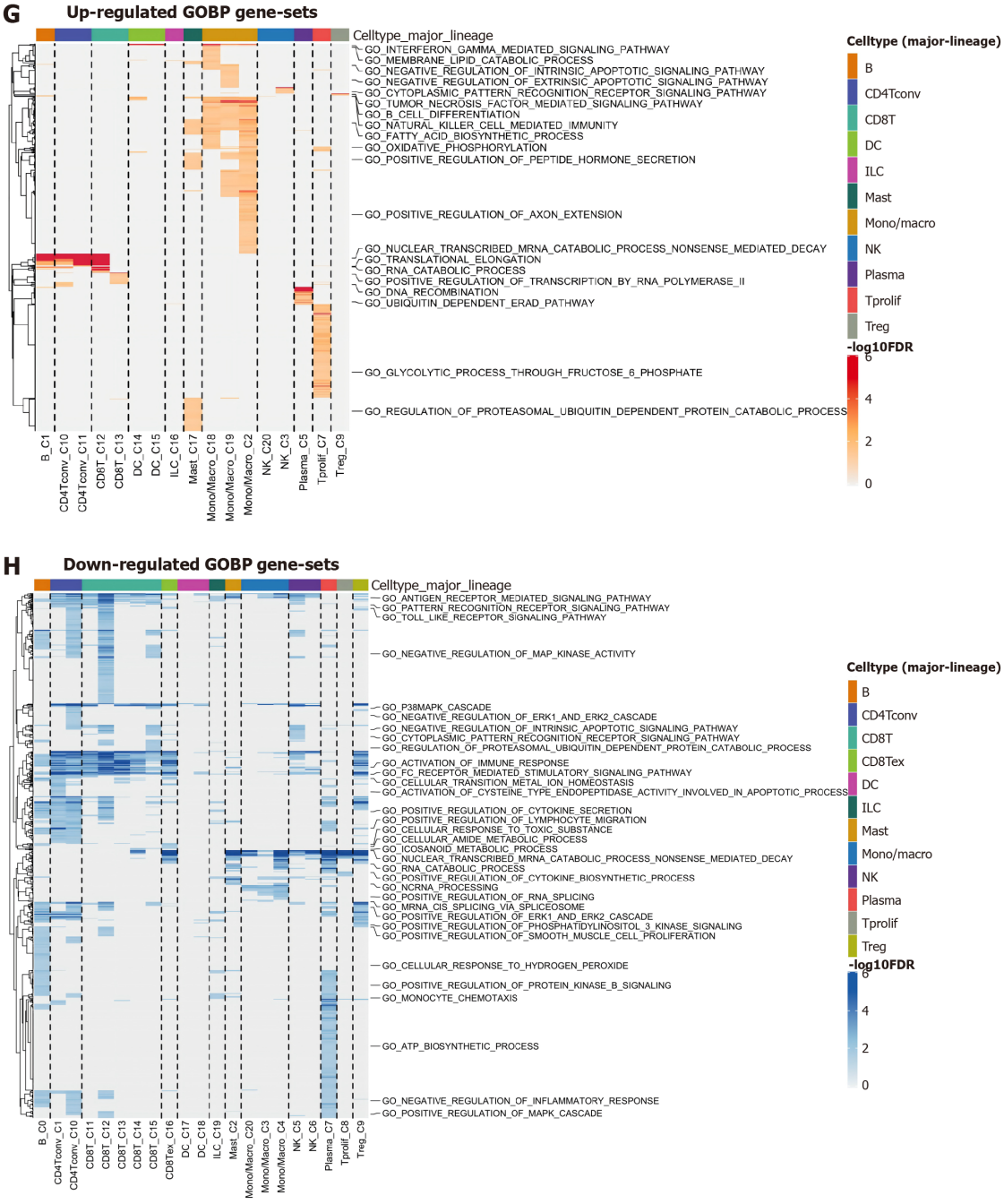
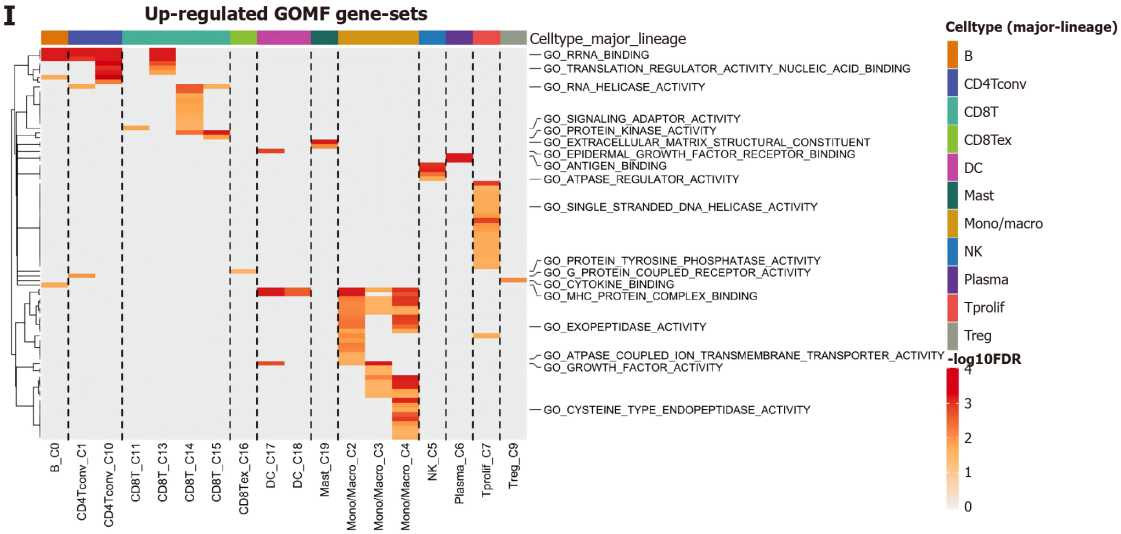
MAPK_SIGNALING_PATHWAY
JAK_STAT_SIGNALING_PATHWAY
CELL_ADHESION_MOLECULES_CAMS
CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION
SPLICEOSOME
RIBOSOME
LYSOSOME
Pathway
B_C7
CD4Tconv_C1
CD4Tconv_C2
CD8T_C0
CD8T_C19
CD8T_C3
CD8T_C4
CD8T_C8
CD8Tex_C6
DC_C14
DC_C17
ILC_C20
Mast_C18
Mono/Macro_C11
Mono/Macro_C13
Mono/Macro_C9
NK_C12
NK_C5
Plasma_C15
Tprolif_C16
Treg_C10
Pathway
Cancer: specific types
Carbohydrate metabolism
Cardiovascular disease
Cell motility
Cellular community - eukaryotes
Circulatory system
Development and regeneration
Endocrine and metabolic disease
Energy metabolism
Immune disease
Immune system
Infectious disease: bacterial
Infectious disease: viral
Nervous system
Neurodegenerative disease
Signal transduction
Signaling molecules and interaction
Transcription
Translation
Transport and catabolism
Celltype (major-lineage)
B
CD4Tconv
CD8T
CD8Tex
DC
ILC
Mast
Mono/Macro
NK
Plasma
Tprolif
Treg
-log10FDR
4
3
2
1
0


G
Up-regulated GOBP gene-sets
Celltype_major_lineage
GO_INTERFERON_GAMMA_MEDIATED_SIGNALING_PATHWAY
GO_MEMBRANE_LIPID_CATABOLIC_PROCESS
GO_NEGATIVE_REGULATION_OF_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY
GO_NEGATIVE_REGULATION_OF_EXTRINSIC_APOPTOTIC_SIGNALING_PATHWAY
GO_CYTOPLASMIC_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY
GO_TUMOR_NECROSIS_FACTOR_MEDIATED_SIGNALING_PATHWAY
GO_B_CELL_DIFFERENTIATION
GO_NATURAL_KILLER_CELL_MEDIATED_IMMUNITY
GO_FATTY_ACID_BIOSYNTHETIC_PROCESS
GO_OXIDATIVE_PHOSPHORYLATION
GO_POSITIVE_REGULATION_OF_PEPTIDE_HORMONE_SECRETION
GO_POSITIVE_REGULATION_OF_AXON_EXTENSION
GO_NUCLEAR_TRANSCRIBED_MRNA_CATABOLIC_PROCESS_NONSENSE_MEDIATED_DECAY
GO_TRANSLATIONAL_ELONGATION
GO_RNA_CATABOLIC_PROCESS
GO_POSITIVE_REGULATION_OF_TRANSCRIPTION_BY_RNA_POLYMERASE_II
GO_DNA_RECOMBINATION
GO_UBIQUITIN_DEPENDENT_ERAD_PATHWAY
GO_GLYCOLYTIC_PROCESS_THROUGH_FRUCTOSE_6_PHOSPHATE
GO_REGULATION_OF_PROTEASOMAL_UBIQUITIN_DEPENDENT_PROTEIN_CATABOLIC_PROCESS
B_C1
CD4Tconv_C10
CD4Tconv_C11
CD8T_C12
CD8T_C13
DC_C14
DC_C15
ILC_C16
Mast_C17
Mono/Macro_C18
Mono/Macro_C19
Mono/Macro_C2
NK_C20
NK_C3
Plasma_C5
Tprolif_C7
Treg_C9
Celltype (major-lineage)
B
CD4Tconv
CD8T
DC
ILC
Mast
Mono/macro
NK
Plasma
Tprolif
Treg
-log10FDR
6
4
2
0

H
Down-regulated GOBP gene-sets
Celltype_major_lineage
GO_ANTIGEN_RECEPTOR_MEDIATED_SIGNALING_PATHWAY
GO_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY
GO_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY
GO_NEGATIVE_REGULATION_OF_MAP_KINASE_ACTIVITY
GO_P38MAPK_CASCADE
GO_NEGATIVE_REGULATION_OF_ERK1_AND_ERK2_CASCADE
GO_NEGATIVE_REGULATION_OF_INTRINSIC_APOPTOTIC_SIGNALING_PATHWAY
GO_CYTOPLASMIC_PATTERN_RECOGNITION_RECEPTOR_SIGNALING_PATHWAY
GO_REGULATION_OF_PROTEASOMAL_UBIQUITIN_DEPENDENT_PROTEIN_CATABOLIC_PROCESS
GO_ACTIVATION_OF_IMMUNE_RESPONSE
GO_FC_RECEPTOR_MEDIATED_STIMULATORY_SIGNALING_PATHWAY
GO_CELLULAR_TRANSITION_METAL_ION_HOMEOSTASIS
GO_ACTIVATION_OF_CYSTEINE_TYPE_ENDOPEPTIDASE_ACTIVITY_INVOLVED_IN_APOPTOTIC_PROCESS
GO_POSITIVE_REGULATION_OF_CYTOKINE_SECRETION
GO_POSITIVE_REGULATION_OF_LYMPHOCYTE_MIGRATION
GO_CELLULAR_RESPONSE_TO_TOXIC_SUBSTANCE
GO_CELLULAR_AMIDE_METABOLIC_PROCESS
GO_ICOSANOID_METABOLIC_PROCESS
GO_NUCLEAR_TRANSCRIBED_MRNA_CATABOLIC_PROCESS_NONSENSE_MEDIATED_DECAY
GO_RNA_CATABOLIC_PROCESS
GO_POSITIVE_REGULATION_OF_CYTOKINE_BIOSYNTHETIC_PROCESS
GO_NCRNA_PROCESSING
GO_POSITIVE_REGULATION_OF_RNA_SPLICING
GO_MRNA_CIS_SPLICING_VIA_SPLICEOSOME
GO_POSITIVE_REGULATION_OF_ERK1_AND_ERK2_CASCADE
GO_POSITIVE_REGULATION_OF_PHOSPHATIDYLINOSITOL_3_KINASE_SIGNALING
GO_POSITIVE_REGULATION_OF_SMOOTH_MUSCLE_CELL_PROLIFERATION
GO_CELLULAR_RESPONSE_TO_HYDROGEN_PEROXIDE
GO_POSITIVE_REGULATION_OF_PROTEIN_KINASE_B_SIGNALING
GO_MONOCYTE_CHEMOTAXIS
GO_ATP_BIOSYNTHETIC_PROCESS
GO_NEGATIVE_REGULATION_OF_INFLAMMATORY_RESPONSE
GO_POSITIVE_REGULATION_OF_MAPK_CASCADE
B_C0
CD4Tconv_C1
CD4Tconv_C10
CD8T_C11
CD8T_C12
CD8T_C13
CD8T_C14
CD8T_C15
CD8Tex_C16
DC_C17
DC_C18
ILC_C19
Mast_C2
Mono/Macro_C20
Mono/Macro_C3
Mono/Macro_C4
NK_C5
NK_C6
Plasma_C7
Tprolif_C8
Treg_C9
Celltype (major-lineage)
B
CD4Tconv
CD8T
CD8Tex
DC
ILC
Mast
Mono/macro
NK
Plasma
Tprolif
Treg
-log10FDR
6
4
2
0


I
Up-regulated GOMF gene-sets
Celltype_major_lineage
GO_RRNA_BINDING
GO_TRANSLATION_REGULATOR_ACTIVITY_NUCLEIC_ACID_BINDING
GO_RNA_HELICASE_ACTIVITY
GO_SIGNALING_ADAPTOR_ACTIVITY
GO_PROTEIN_KINASE_ACTIVITY
GO_EXTRACELLULAR_MATRIX_STRUCTURAL_CONSTITUENT
GO_EPIDERMAL_GROWTH_FACTOR_RECEPTOR_BINDING
GO_ANTIGEN_BINDING
GO_ATPASE_REGULATOR_ACTIVITY
GO_SINGLE_STRANDED_DNA_HELICASE_ACTIVITY
GO_PROTEIN_TYROSINE_PHOSPHATASE_ACTIVITY
GO_G_PROTEIN_COUPLED_RECEPTOR_ACTIVITY
GO_CYTOKINE_BINDING
GO_MHC_PROTEIN_COMPLEX_BINDING
GO_EXOPEPTIDASE_ACTIVITY
GO_ATPASE_COUPLED_ION_TRANSMEMBRANE_TRANSPORTER_ACTIVITY
GO_GROWTH_FACTOR_ACTIVITY
GO_CYSTEINE_TYPE_ENDOPEPTIDASE_ACTIVITY
B_C0
CD4Tconv_C1
CD4Tconv_C10
CD8T_C11
CD8T_C13
CD8T_C14
CD8T_C15
CD8Tex_C16
DC_C17
DC_C18
Mast_C19
Mono/Macro_C2
Mono/Macro_C3
Mono/Macro_C4
NK_C5
Plasma_C6
Tprolif_C7
Treg_C9
Celltype (major-lineage)
B
CD4Tconv
CD8T
CD8Tex
DC
Mast
Mono/macro
NK
Plasma
Tprolif
Treg
-log10FDR
4
3
2
1
0

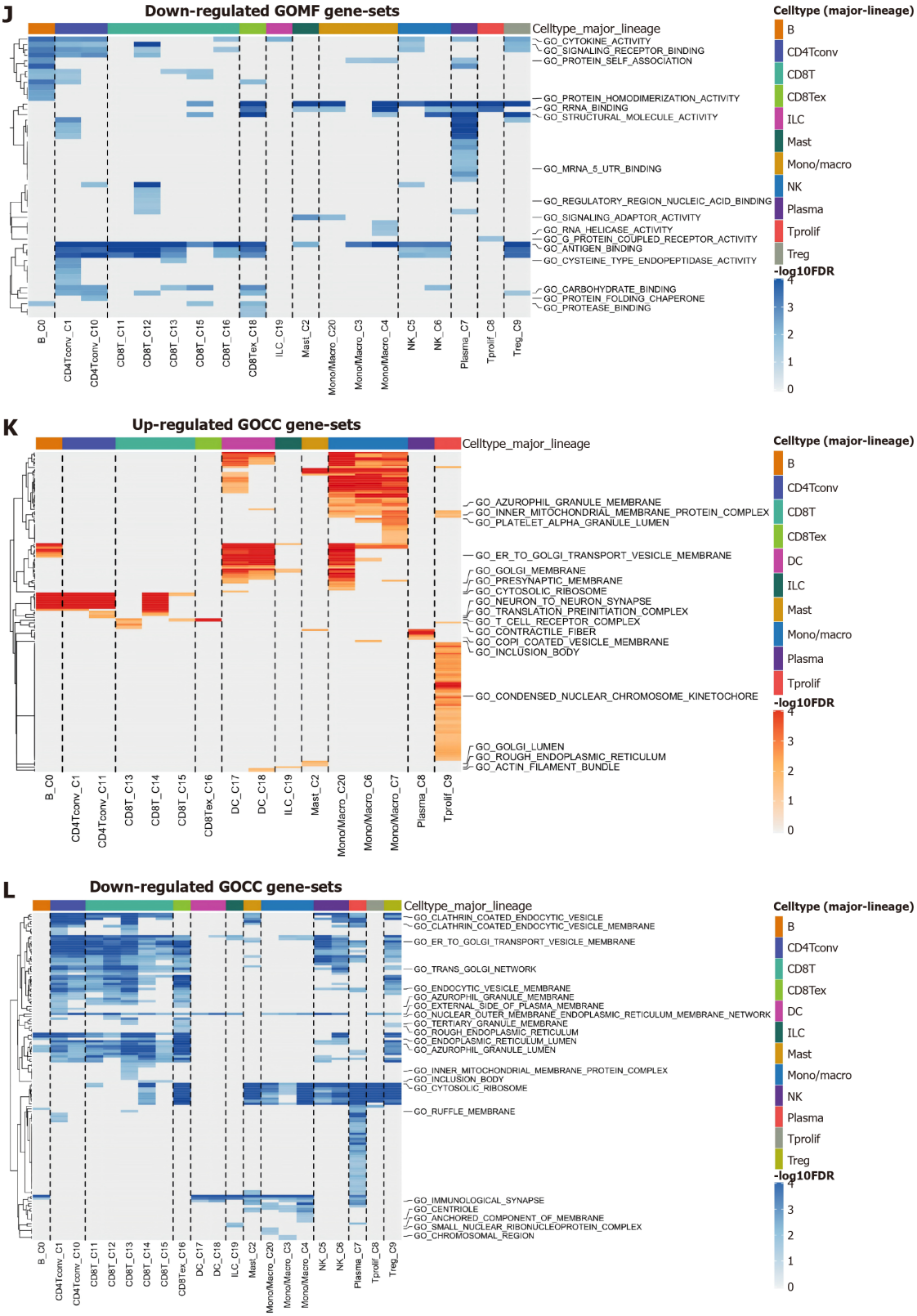
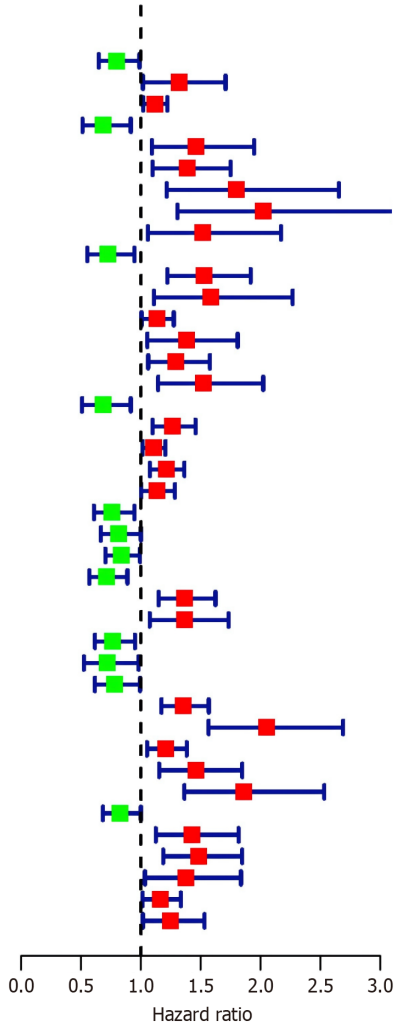


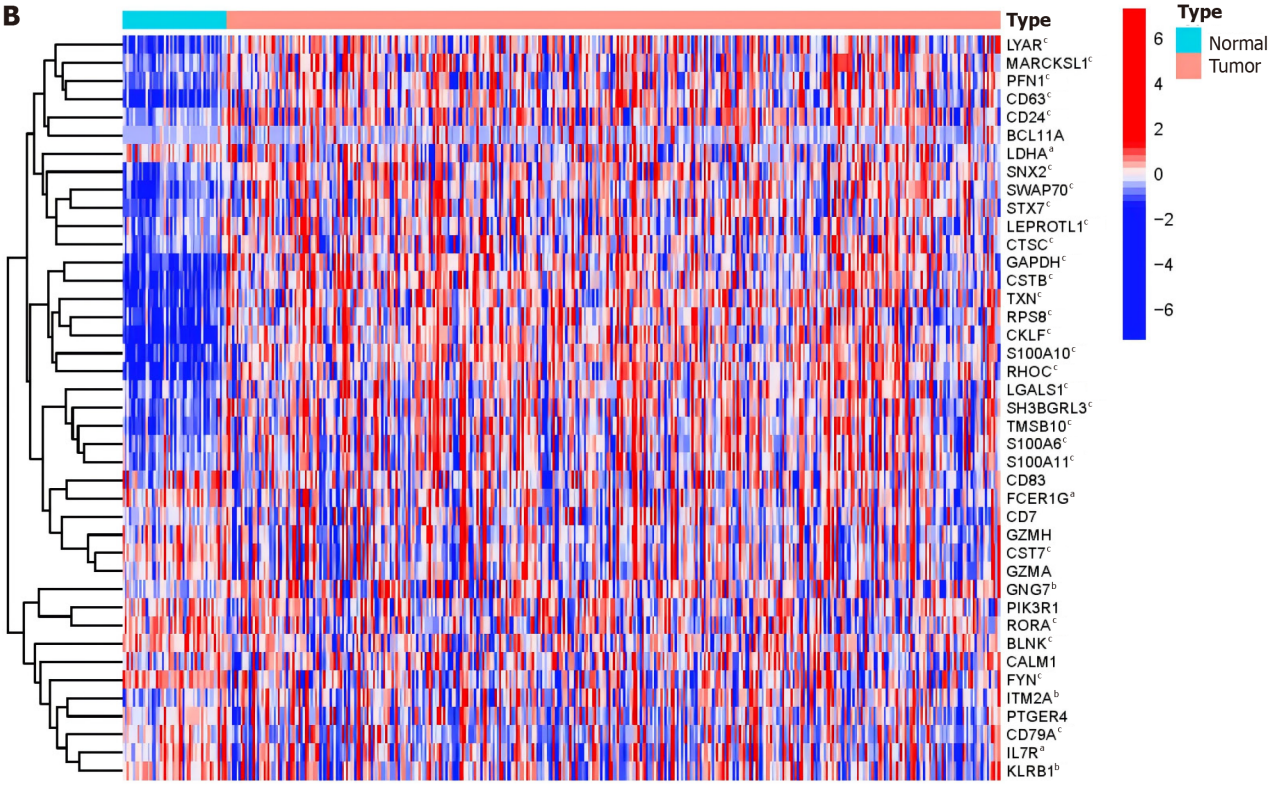
Figure 3 Analysis of B-cell-related immune signatures in hepatocellular carcinoma. A: Heatmap illustrates key transcription factors differentially expressed in various cells within hepatocellular carcinoma (HCC); B: Dot plot displays significantly expressed transcription factors in B cells of HCC; C: Heatmap shows immunological gene sets positively regulated by each cell subgroup; D: Heatmap displays immunological gene sets negatively regulated by each cell subgroup; E: Heatmap exhibits Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment pathways positively regulated by each cell subgroup; F: Heatmap exhibits KEGG enrichment pathways negatively regulated by each cell subgroup; G: Heatmap displays gene ontology biological process (GOBP) enrichment pathways positively regulated by each cell subgroup; H: Heatmap displays GOBP enrichment pathways negatively regulated by each cell subgroup; I: Heatmap displays gene ontology molecular function (GOMF) enrichment pathways positively regulated by each cell subgroup; J: Heatmap displays GOMF enrichment pathways negatively regulated by each cell subgroup; K: Heatmap displays gene ontology cellular component (GOCC) enrichment pathways positively regulated by each cell subgroup; L: Heatmap displays GOCC enrichment pathways negatively regulated by each cell subgroup.

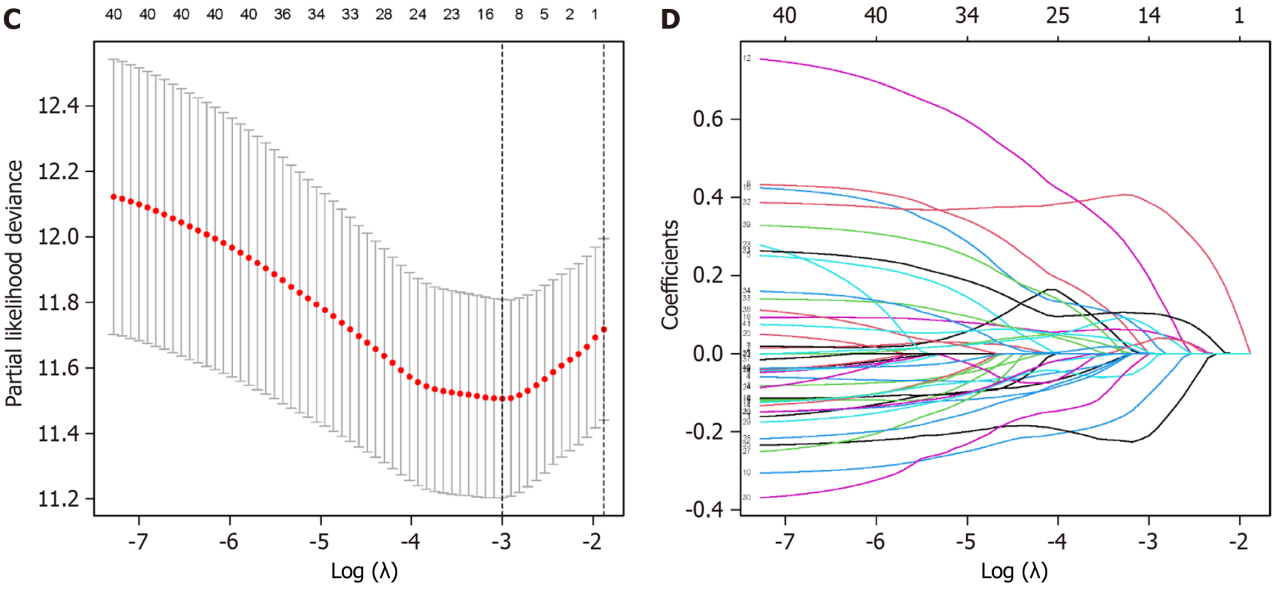
A

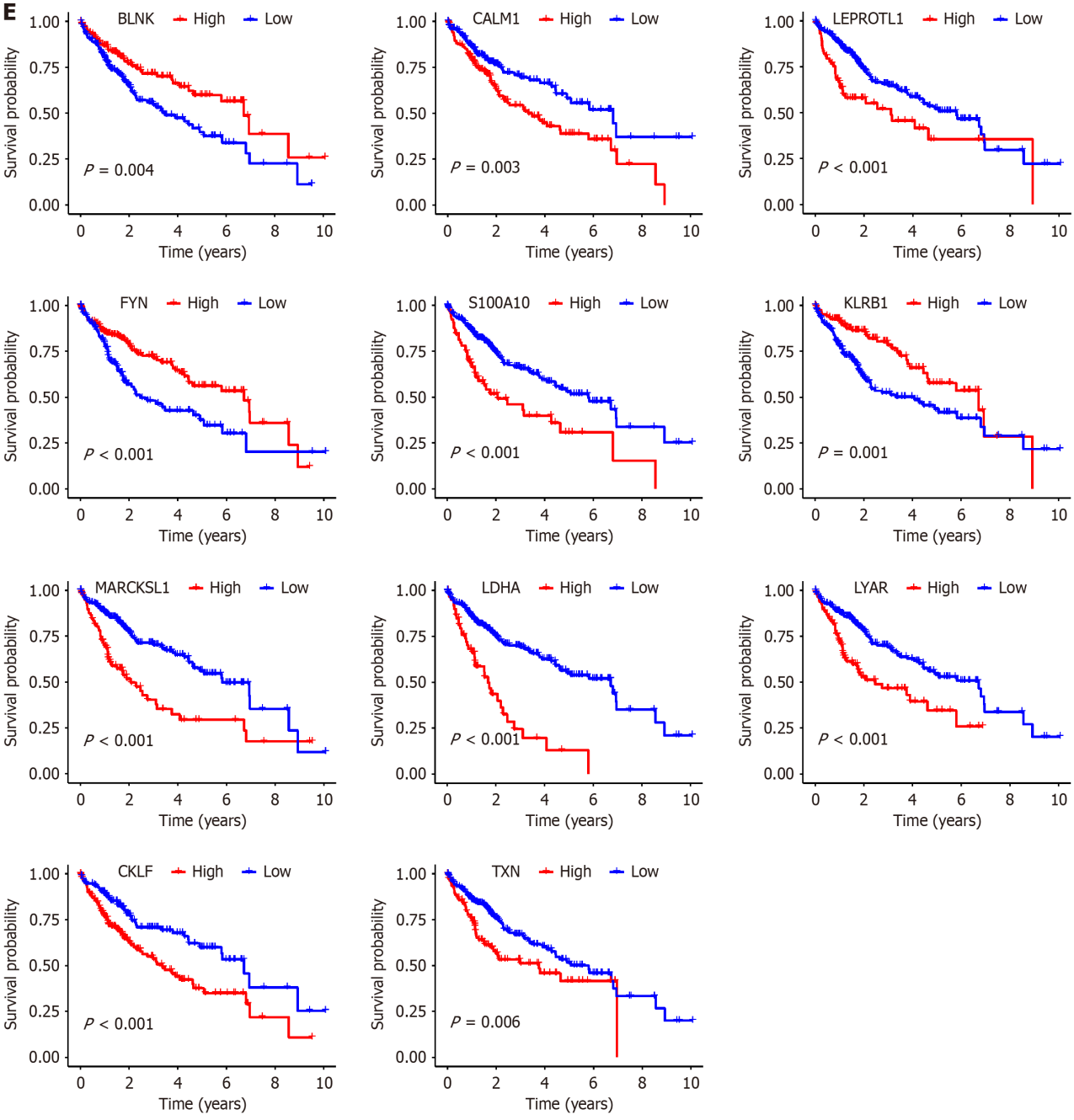
	P value	Hazard ratio
CD79A	0.037	0.799 (0.646−0.987)
CD83	0.037	1.317 (1.016−1.706)
CD24	0.017	1.116 (1.020−1.222)
GNG7	0.011	0.684 (0.511−0.915)
SWAP70	0.011	1.457 (1.092−1.945)
RPS8	0.006	1.385 (1.096−1.749)
SNX2	0.003	1.794 (1.214−2.651)
BCL11A	0.002	2.019 (1.305−3.124)
STX7	0.023	1.516 (1.059−2.170)
BLNK	0.018	0.724 (0.553−0.946)
GAPDH	< 0.001	1.529 (1.221−1.915)
CALM1	0.012	1.585 (1.108−2.267)
TMSB10	0.041	1.132 (1.005−1.274)
PFN1	0.019	1.380 (1.054−1.807)
SH3BGRL3	0.011	1.293 (1.060−1.576)
LEPROTL1	0.004	1.521 (1.144−2.021)
FYN	0.011	0.683 (0.509−0.915)
S100A10	0.001	1.264 (1.097−1.455)
S100A6	0.022	1.106 (1.015−1.205)
S100A11	0.002	1.210 (1.074−1.363)
CD7	0.045	1.134 (1.003−1.284)
IL7R	0.014	0.757 (0.607−0.945)
CST7	0.049	0.816 (0.666−0.999)
GZMA	0.040	0.835 (0.703−0.992)
KLRB1	0.003	0.710 (0.569−0.887)
CTSC	< 0.001	1.364 (1.147−1.622)
CD63	0.011	1.363 (1.073−1.732)
PIK3R1	0.015	0.765 (0.616−0.950)
RORA	0.037	0.716 (0.524−0.980)
GZMH	0.043	0.781 (0.615−0.993)
MARCKSL1	< 0.001	1.355 (1.171−1.566)
LDHA	< 0.001	2.051 (1.565−2.687)
FCER1G	0.008	1.205 (1.050−1.382)
CSTB	0.002	1.458 (1.152−1.846)
LYAR	< 0.001	1.857 (1.363−2.530)
ITM2A	0.049	0.825 (0.682−0.999)
RHOC	0.004	1.428 (1.123−1.815)
CKLF	< 0.001	1.480 (1.186−1.845)
PTGER4	0.029	1.377 (1.033−1.835)
LGALS1	0.029	1.163 (1.015−1.333)
TXN	0.035	1.247 (1.016−1.530)



B




C
40 40 40 40 40 36 34 33 28 24 23 16 8 5 2 1
Partial likelihood deviance
12.4
12.2
12.0
11.8
11.6
11.4
11.2
-7 -6 -5 -4 -3 -2
Log (λ)
D
40 40 34 25 14 1
Coefficients
0.6
0.4
0.2
0.0
-0.2
-0.4
-7 -6 -5 -4 -3 -2
Log (λ)


E
BLNK High Low
P = 0.004
CALM1 High Low
P = 0.003
LEPROTL1 High Low
P < 0.001
FYN High Low
P < 0.001
S100A10 High Low
P < 0.001
KLRB1 High Low
P = 0.001
MARCKSL1 High Low
P < 0.001
LDHA High Low
P < 0.001
LYAR High Low
P < 0.001
CKLF High Low
P < 0.001
TXN High Low
P = 0.006
Survival probability
1.00
0.75
0.50
0.25
0.00
0 2 4 6 8 10
Time (years)

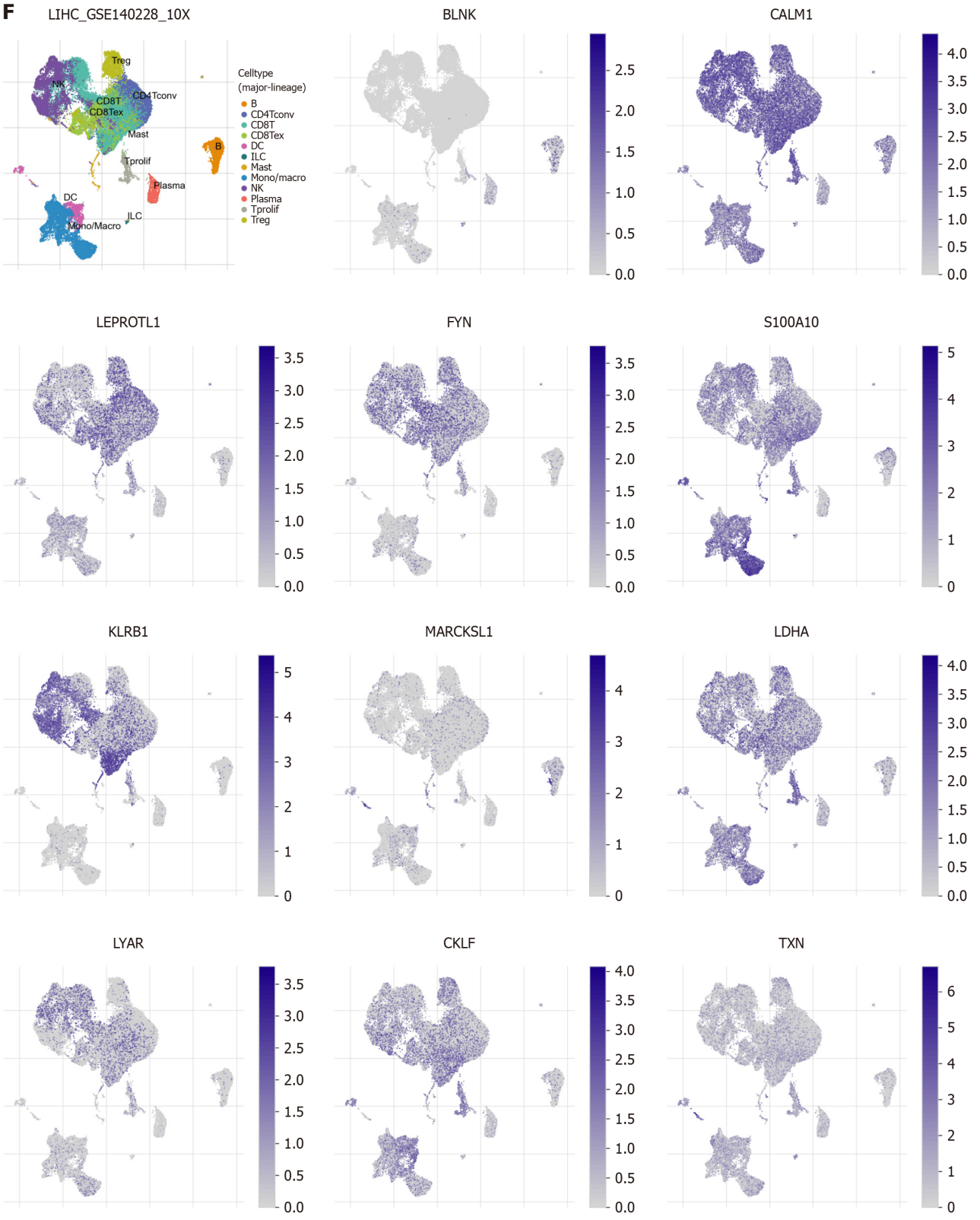
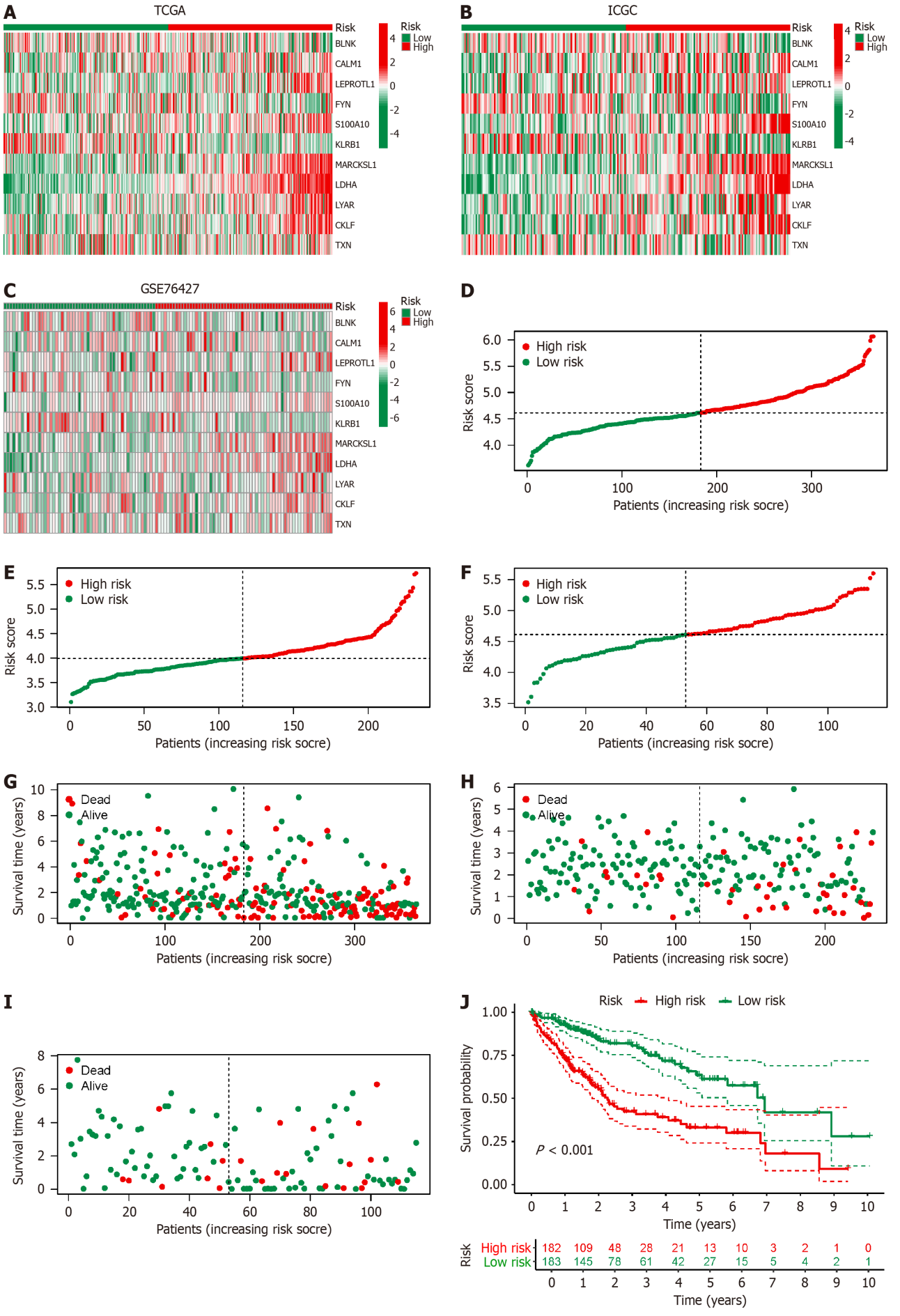


Figure 4 Establishment of prognostic model of B-cell-related genes in hepatocellular carcinoma. A: Forest plot displays B-cell-related genes (BRGs) associated with hepatocellular carcinoma (HCC) prognosis, green indicates hazard ratio < 1, red indicates hazard ratio > 1; B: Heatmap illustrates the expression levels of BRGs associated with HCC prognosis in both HCC and paired adjacent non-tumor samples; C: Least absolute shrinkage and selection operator (LASSO) regression analysis cross-validation curve demonstrates the fitting effect of the model when incorporating different numbers of BRGs; D: LASSO coefficient path plot displays the lambda values when the model incorporates different numbers of BRGs; E: Survival analysis depicts the relationship between the expression levels of 11 BRGs included in the prognostic model and the prognosis of HCC patients; F: Single-cell analysis reveals the expression levels of the 11 BRGs included in the prognostic model within B cells of HCC. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$.


A
TCGA
B
ICGC
C
GSE76427
Risk
Low
High
BLNK
CALM1
LEPROTL1
FYN
S100A10
KLRB1
MARCKSL1
LDHA
LYAR
CKLF
TXN
D
E
F
High risk
Low risk
Risk score
Patients (increasing risk socre)
G
H
I
Dead
Alive
Survival time (years)
J
Risk
High risk
Low risk
Survival probability
P < 0.001
Time (years)
182 109 48 28 21 13 10 3 2 1 0
183 145 78 61 42 27 15 5 4 2 1

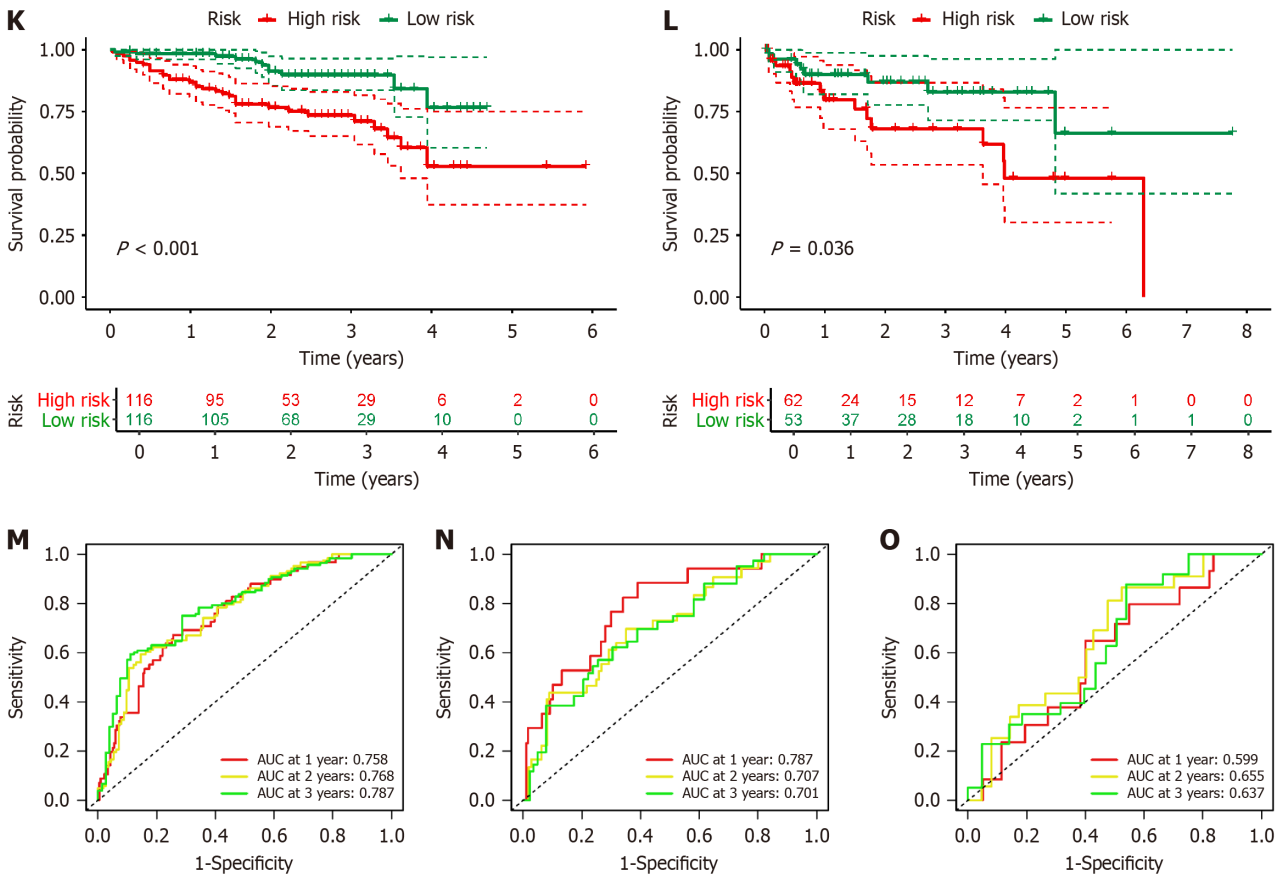
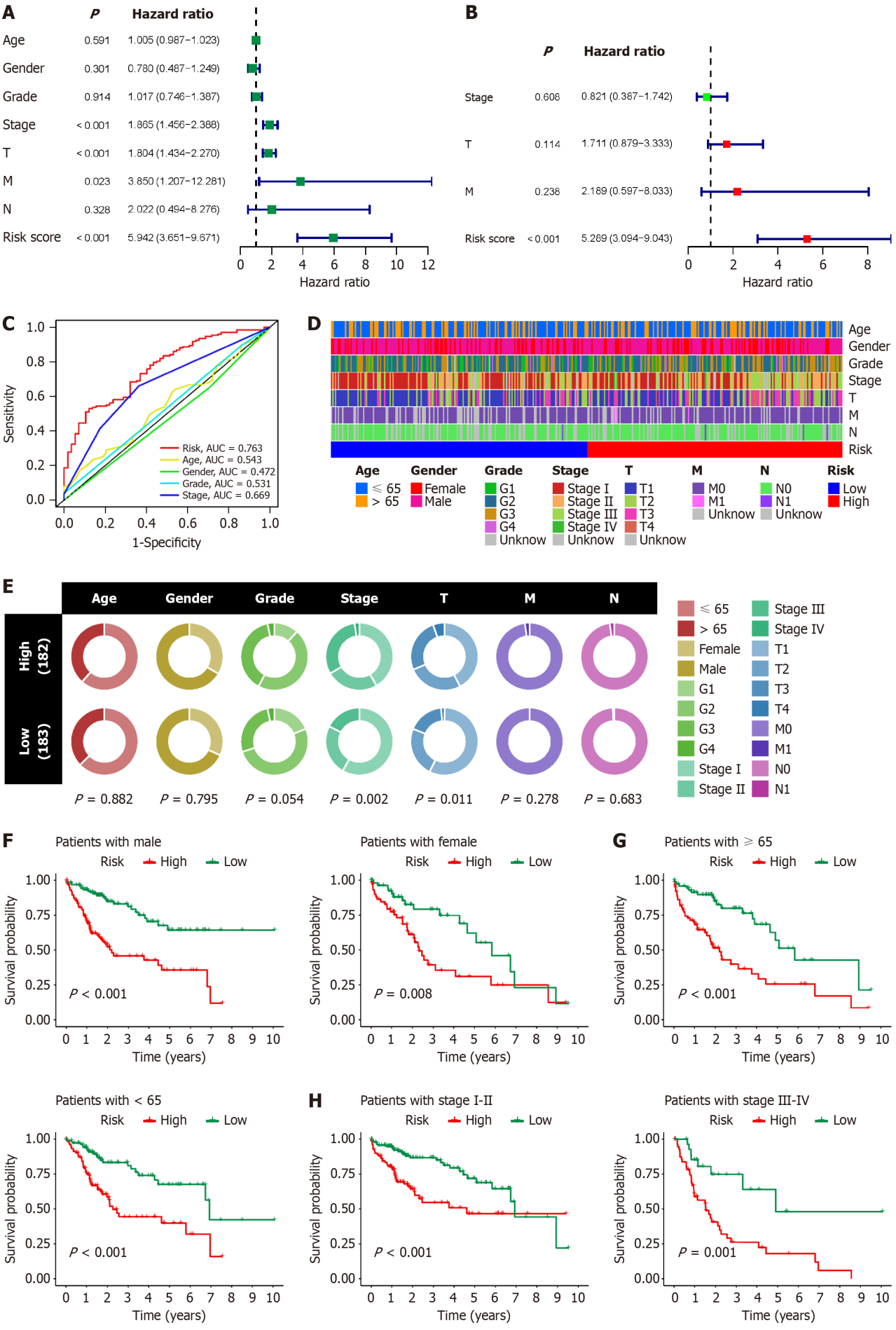


Figure 5 Validation of B-cell-related genes prognostic model in hepatocellular carcinoma. A–C: Heatmap displays the expression levels of the 11 B-cell-related genes (BRGs) included in the prognostic model in The Cancer Genome Atlas (TCGA) (A); International Cancer Genome Consortium (ICGC) (B); Gene set enrichment (GSE) 76427 (C); D–F: Risk curves depict the distribution of hepatocellular carcinoma (HCC) patients with different risk scores in TCGA (D); ICGC (E); GSE76427 (F); G–I: Dot plots show the distribution of the survival status of HCC patients with different risk scores in TCGA (G); ICGC (H); GSE76427 (I); J–L: Survival curves illustrate the prognosis of HCC patients with different risk scores in TCGA (J); ICGC (K); GSE76427 (L); M–O: Receiver operating characteristic curves demonstrate the predictive efficacy of the BRGs prognostic model in TCGA (M); ICGC (N); GSE76427 (O); AUC: Areas under the curves.

Cox regression analysis revealed that the stage, T stage, M stage, and risk score of HCC were significant factors associated with poor prognosis, with risk score exhibiting the highest hazard ratio (Figure 6A). Multifactor Cox regression analysis indicated that risk score was the sole independent prognostic factor for HCC, suggesting its potential for accurate stand-alone diagnosis of HCC (Figure 6B). Compared with clinically common factors such as age, gender, grade, and stage in assessing HCC prognosis, risk score demonstrated significantly higher AUC values, underscoring the substantial advantages and efficacy of the BRGs prognostic model in evaluating HCC prognosis (Figure 6C). We also assessed the correlation between risk score and clinicopathological factors, revealing that HCC with high risk score had higher stages and T stages, while risk score showed no significant correlation with age, gender, grade, M stage, or N stage of HCC patients (Figure 6D and E). We further evaluated the value of the BRGs prognostic model in different clinical subgroups by stratifying HCC patients into different clinical subsets based on age, gender, grade, and stage. The results demonstrated that patients in the high-risk score group exhibited poorer prognosis across all clinical subsets (Figure 6F–I). These findings underscore the significant value and potential of the BRGs prognostic model in clinical diagnosis and predicting the prognosis of HCC patients.

Functional enrichment in different risk score groups for HCC

To delve into the distinct features of various risk score groups and elucidate the potential role of B cells in regulating HCC, we conducted differential gene expression analysis on different risk score groups within the TCGA-LIHC dataset. We identified 420 upregulated and 28 downregulated genes (Figure 7A), with the top 50 differentially expressed genes in TCGA-LIHC displayed (Figure 7B). Subsequently, KEGG enrichment analysis was performed to identify differential pathways within different risk score groups. Pathways such as extracellular matrix (ECM)–receptor interaction, central carbon metabolism in cancer, protein digestion and absorption, hypoxia-inducible factor (HIF)-1 signaling pathway, biosynthesis of amino acids, and fructose and mannose metabolism were significantly enriched with differential genes (Figure 7C). Further GO analysis suggested that B cells were involved in crucial cellular molecular functions and biological processes in HCC, including ECM organization, apical part of cells, and G-protein-coupled receptor binding (Figure 7D and E). Lastly, GSEA was conducted to validate the significance of the enriched pathways. Results indicated that in the high-risk score group, KEGG cell cycle and KEGG ECM–receptor interaction were potentially important enriched pathways (Figure 7F), whereas in the low-risk score group, it was KEGG butanoate metabolism and KEGG fatty


A
P
Hazard ratio
Age 0.591 1.005 (0.987–1.023)
Gender 0.301 0.780 (0.487–1.249)
Grade 0.914 1.017 (0.746–1.387)
Stage < 0.001 1.865 (1.456–2.388)
T < 0.001 1.804 (1.434–2.270)
M 0.023 3.850 (1.207–12.281)
N 0.328 2.022 (0.494–8.276)
Risk score < 0.001 5.942 (3.651–9.671)
0 2 4 6 8 10 12
Hazard ratio
B
P
Hazard ratio
Stage 0.608 0.821 (0.387–1.742)
T 0.114 1.711 (0.879–3.333)
M 0.238 2.189 (0.597–8.033)
Risk score < 0.001 5.289 (3.094–9.043)
0 2 4 6 8
Hazard ratio
C
Sensitivity
1-Specificity
Risk, AUC = 0.763
Age, AUC = 0.543
Gender, AUC = 0.472
Grade, AUC = 0.531
Stage, AUC = 0.669
D
Age
Gender
Grade
Stage
T
M
N
Risk
Age ⩽ 65 > 65
Gender Female Male
Grade G1 G2 G3 G4 Unknow
Stage Stage I Stage II Stage III Stage IV Unknow
T T1 T2 T3 T4 Unknow
M M0 M1 Unknow
N N0 N1 Unknow
Risk Low High
E
Age Gender Grade Stage T M N
High (182)
Low (183)
P = 0.882 P = 0.795 P = 0.054 P = 0.002 P = 0.011 P = 0.278 P = 0.683
⩽ 65 > 65 Female Male G1 G2 G3 G4 Stage I Stage II Stage III Stage IV T1 T2 T3 T4 M0 M1 N0 N1
F
Patients with male
Risk High Low
P < 0.001
Patients with female
Risk High Low
P = 0.008
G
Patients with ⩾ 65
Risk High Low
P < 0.001
Patients with < 65
Risk High Low
P < 0.001
H
Patients with stage I-II
Risk High Low
P < 0.001
Patients with stage III-IV
Risk High Low
P = 0.001
Survival probability
Time (years)

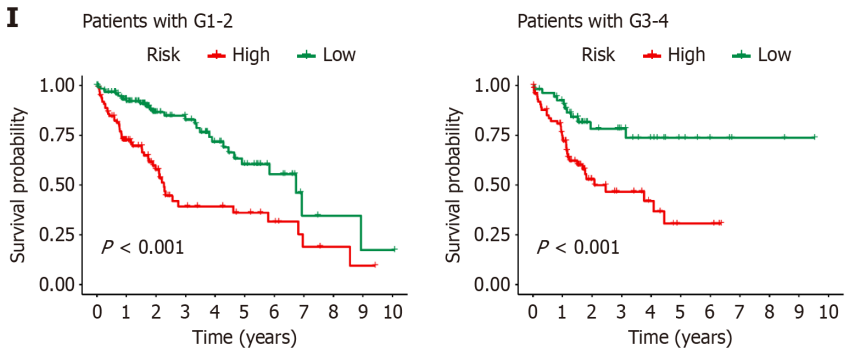


Figure 6 Clinical correlation analysis of B-cell-related genes prognostic model in hepatocellular carcinoma. A: Single-factor Cox regression analysis shows the association between risk score and other clinicopathological factors of hepatocellular carcinoma (HCC) with prognosis; B: Multifactor Cox regression analysis demonstrates whether risk score and other clinicopathological factors of HCC can serve as independent prognostic factors for HCC; C: Receiver operating characteristic curve illustrates the effectiveness of risk score and other clinicopathological factors of HCC in predicting the prognosis of HCC patients; D: Heatmap displays the distribution of various clinical and pathological statuses of HCC patients in different risk score groups; E: Bubble plot demonstrates the proportions of various clinical and pathological statuses among HCC patients in different risk score groups and their correlation with risk score; F–I: Survival analysis shows the ability of the B-cell-related genes prognostic model to predict the prognosis of HCC patients in various clinical subgroups. AUC: Areas under the curves.

acid metabolism (Figure 7G).

The mutation of key genes in tumor cells is closely associated with the progression and prognosis of HCC[19]. We sought to determine whether the functionality of B cells in HCC correlates with this. Patients with HCC in the high-risk score group exhibited significantly higher somatic mutation rates in key genes, such as *TP53* (33% *vs* 19%) and *TTN* (27% *vs* 20%), compared with those in the low-risk score group (Figure 7H and I). HCC patients with a high tumor mutation burden (TMB) had significantly poorer prognosis than those with a low TMB (Figure 7J). When evaluating the prognosis of HCC patients using both TMB and risk score, those with high TMB and high risk scores had the worst prognosis. Conversely, those with low TMB and low risk scores had the best prognosis. Patients with either high TMB or high risk scores alone had prognoses that fell between these extremes (Figure 7K). These results suggest that the functionality of B cells in HCC is associated with somatic mutations and that the BRGs prognosis model, when combined with TMB, can enhance the prediction of prognosis in HCC patients.

Assessment of immune microenvironment in different risk score groups of HCC

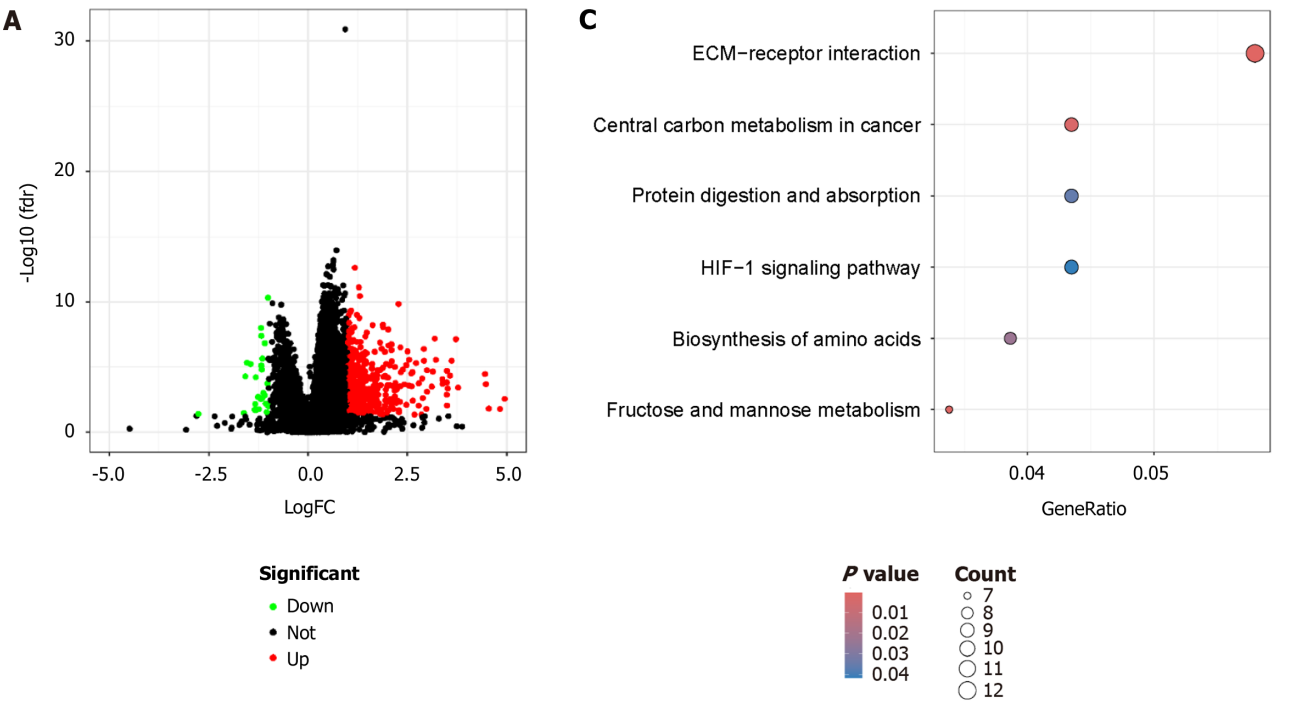
B cells, as crucial immune cells, are likely to play a significant role in the regulation of the immune microenvironment in HCC. Regarding immune microenvironment analysis, patients with HCC in the high-risk score group showed a trend towards decreased stromal score ($P = 0.063$), immune score ($P = 0.056$), and estimate score ($P = 0.051$), although the lack of significant differences may be attributed to the small sample size (Figure 8A–C). Concerning immune cell infiltration, there was a significant negative correlation between risk score and B-cell infiltration, with various types of T cells showing a similar trend to B cells (Figure 8D). ssGSEA algorithm or CIBERSORT algorithm both revealed significantly suppressed B-cell infiltration in patients with high risk scores, with T cells exhibiting a similar infiltration pattern (Figure 8E–G). These findings align with those shown in Figures 2 and 3, indicating a probable collaboration between B cells and T cells in HCC. Based on the ssGSEA algorithm, we also observed significant suppression of functions related to cytolytic activity, inflammation promotion, T-cell co-inhibition, and T-cell co-stimulation in high-risk patients (Figure 8H), further corroborating our standpoint.

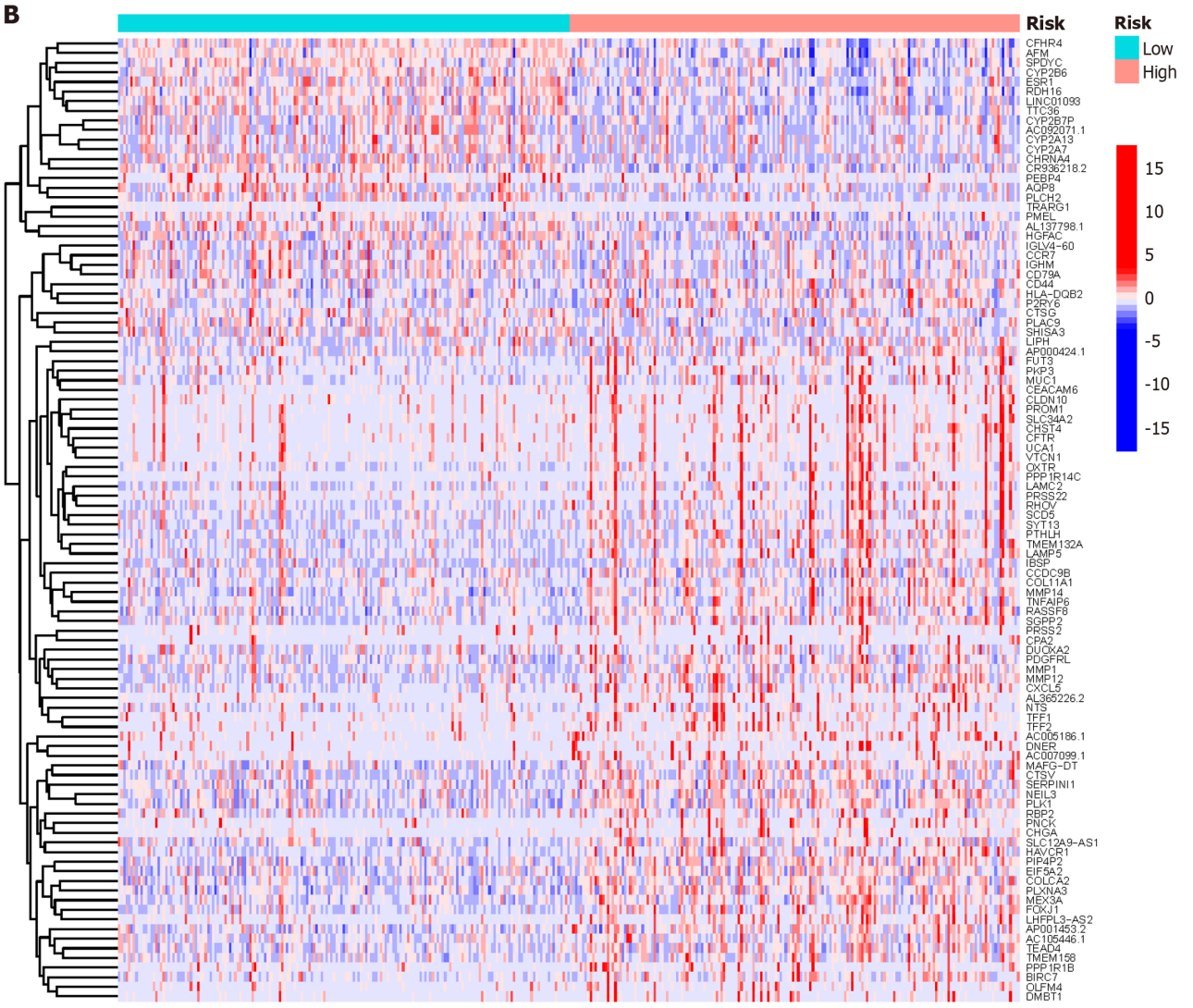
BRGs prognostic model and TCGA official immune typing

The TCGA official team has classified HCC into four subtypes: (1) Wound Healing (Immune C1); (2) Interferon- dominant (Immune C2); (3) Inflammatory (Immune C3); and (4) Lymphocyte depleted (Immune C4), which has become a significant reference for classification[20]. Our findings indicate that the BRGs prognosis model can differentiate immune subtypes, particularly with a notable increase in the number of Immune C1 patients with high-risk scores and a marked decrease in the number of Immune C3 patients (Figure 8I).

BRGs prognostic model evaluates immunotherapy efficacy

Our findings indicate that the BRGs prognosis model can differentiate immune subtypes, particularly with a notable increase in the number of Immune C1 patients with high-risk scores and a marked decrease in the number of Immune C3 patients (Figure 8I). Immune checkpoints, crucial factors expressed on immune cells capable of modulating immune activation levels, play a pivotal role. These genes, under normal circumstances, can inhibit T-cell function to prevent excessive immune system activation. Simultaneously, in tumor tissues, they might be exploited by tumors to facilitate immune evasion. The effectiveness of immune checkpoint inhibitors in treating HCC has been demonstrated[21,22]. Our analysis suggests that in the high-risk score group, expression of most immune checkpoint genes (17 of 25) significantly increased (Figure 8J), indicating that patients in the high-risk score group may benefit from these immune checkpoint inhibitors. *ENTPD1*, *NT5E*, and *HAVCR2* are also immune checkpoint genes coexpressed at high levels in both B cells and T cells[23], further indicating potential synergistic action between B cells and T cells in HCC. We evaluated the efficacy of


A
30
20
10
0
-Log10 (fdr)
-5.0
-2.5
0.0
2.5
5.0
LogFC
Significant
Down
Not
Up
C
ECM−receptor interaction
Central carbon metabolism in cancer
Protein digestion and absorption
HIF−1 signaling pathway
Biosynthesis of amino acids
Fructose and mannose metabolism
0.04
0.05
GeneRatio
P value
0.01
0.02
0.03
0.04
Count
7
8
9
10
11
12


B
Risk
Risk
Low
High
15
10
5
0
-5
-10
-15
CFHR4
AFM
SPDYC
CYP2B6
ESR1
RDH16
LINC01093
TTC36
CYP2B7P
AC092071.1
CYP2A13
CYP2A7
CHRNA4
CR936218.2
PEBP4
AQP8
PLCH2
TRARG1
PMEL
AL137798.1
HGFAC
IGLV4−60
COR7
IGHM
CD79A
CD44
HLA−DQB2
P2RY6
CTSG
PLAC9
SHISA3
LIPH
AP000424.1
FUT3
PKP3
MUC1
CEACAM6
CLDN10
PROM1
SLC34A2
CHST4
CFTR
UCA1
VTCN1
OXTR
PPP1R14C
LAMC2
PRSS22
RHOV
SCD5
SYT13
PTHLH
TMEM132A
LAMP5
IBSP
CCDC9B
COL11A1
MMP14
TNFAIP6
RASSF8
SGPP2
PRSS2
CPA2
DUOXA2
PDGFRL
MMP1
MMP12
CXCL5
AL365226.2
NTS
TFF1
TFF2
AC005186.1
DNER
AC007099.1
MAFG−DT
CTSV
SERPINI1
NEIL3
PLK1
RBP2
PNCK
CHGA
SLC12A9−AS1
HAVCR1
PIP4P2
EIF5A2
COLCA2
PLXNA3
MEX3A
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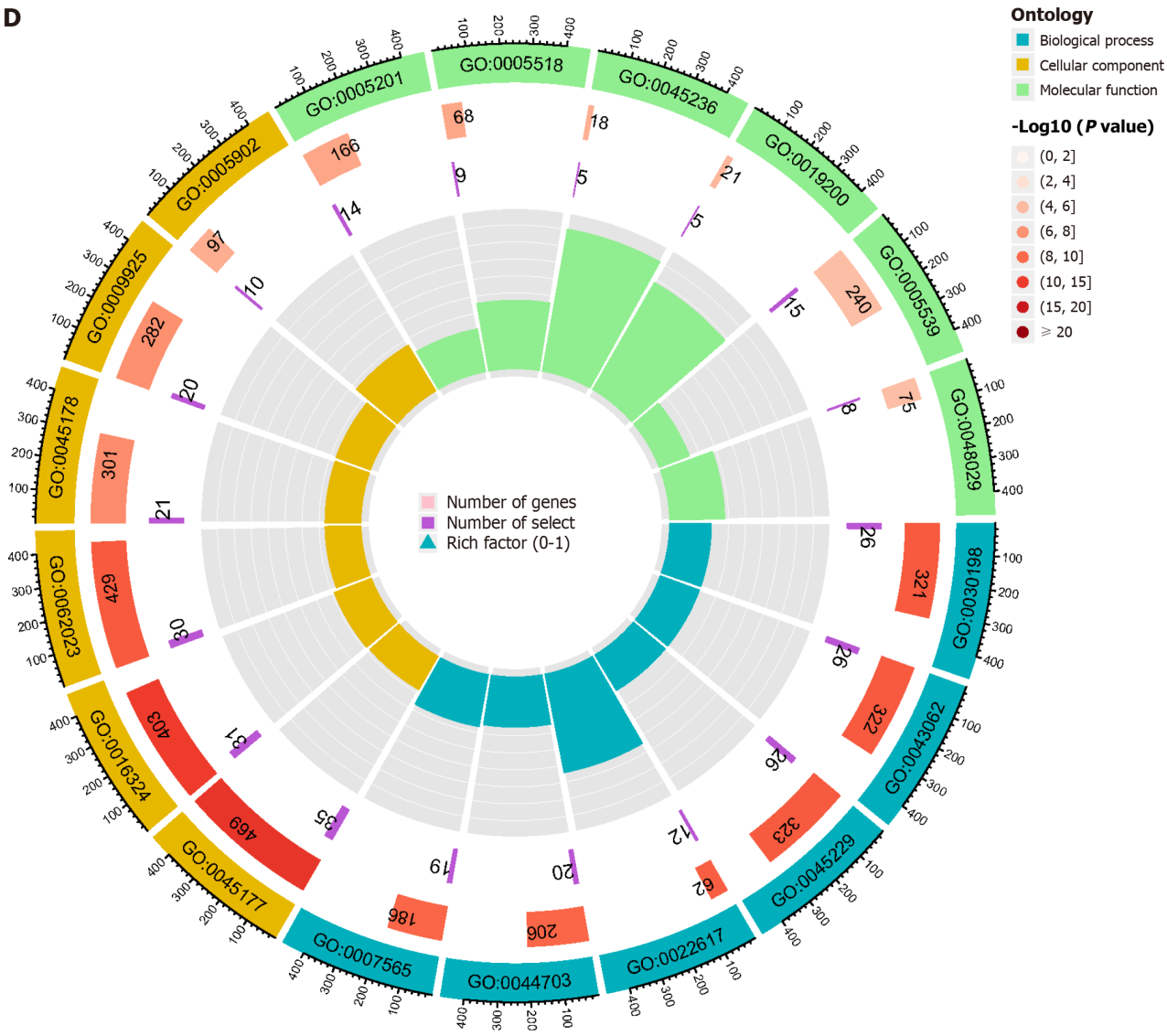
BIRC7
OLFM4
DMBT1


D
Ontology
Biological process
Cellular component
Molecular function
-Log10 (P value)
(0, 2]
(2, 4]
(4, 6]
(6, 8]
(8, 10]
(10, 15]
(15, 20]
⩾ 20
Number of genes
Number of select
Rich factor (0-1)
GO:0005518
GO:0045236
GO:0019200
GO:0005539
GO:0048029
GO:0030198
GO:0043062
GO:0045229
GO:0022617
GO:0044703
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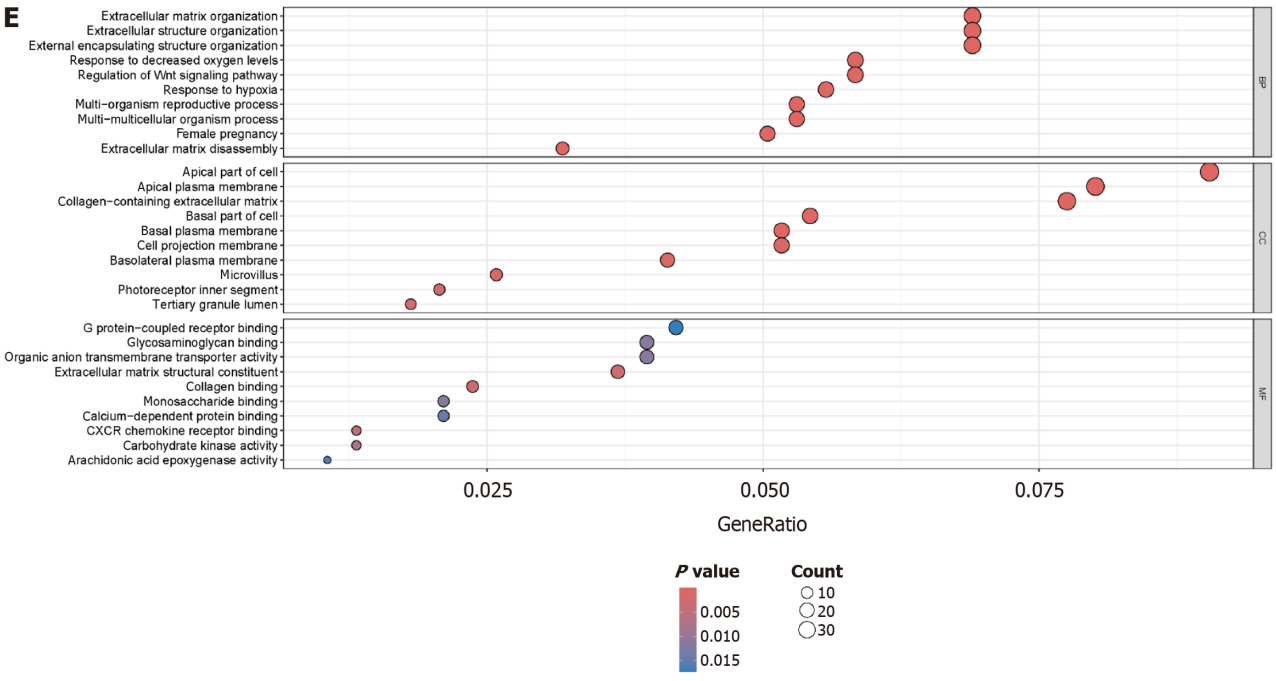
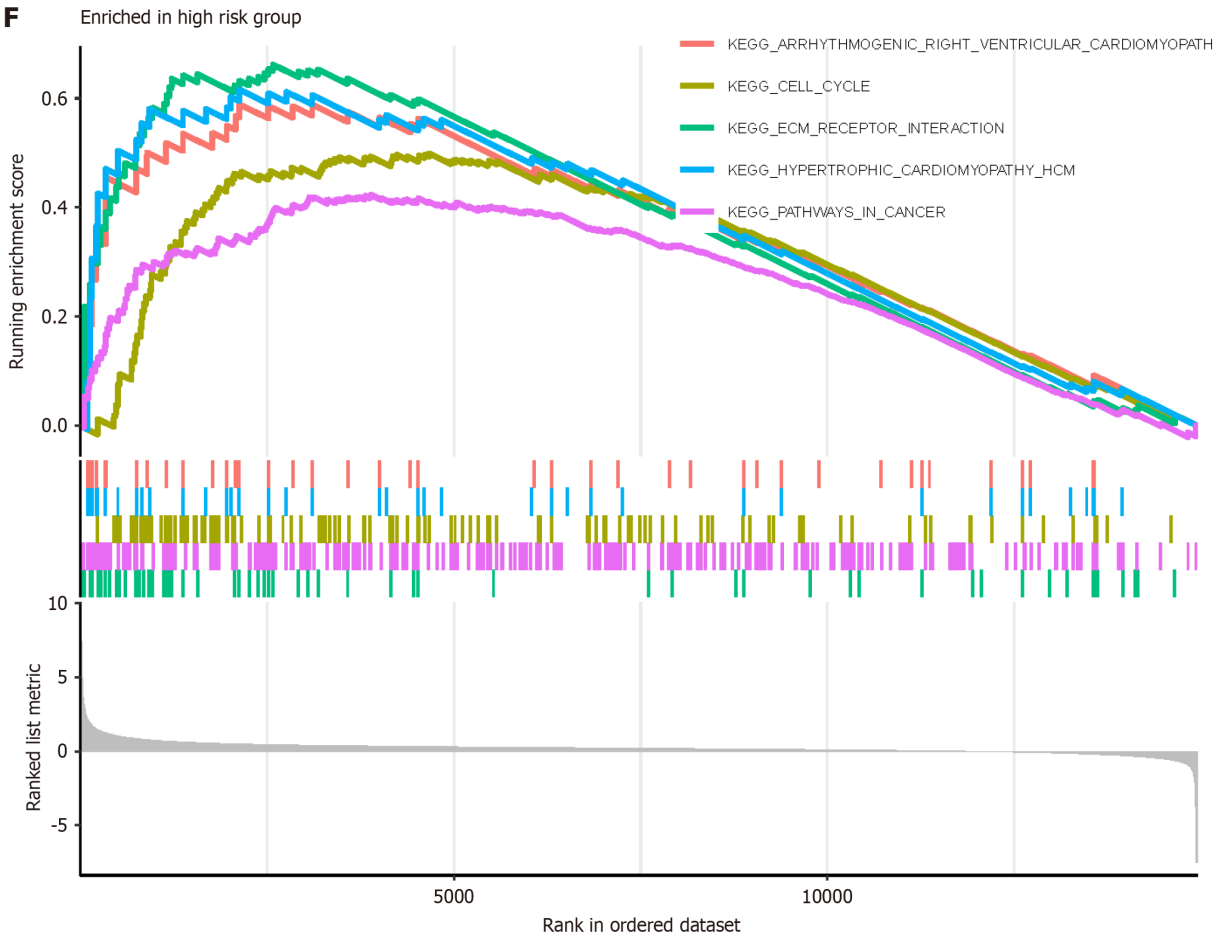
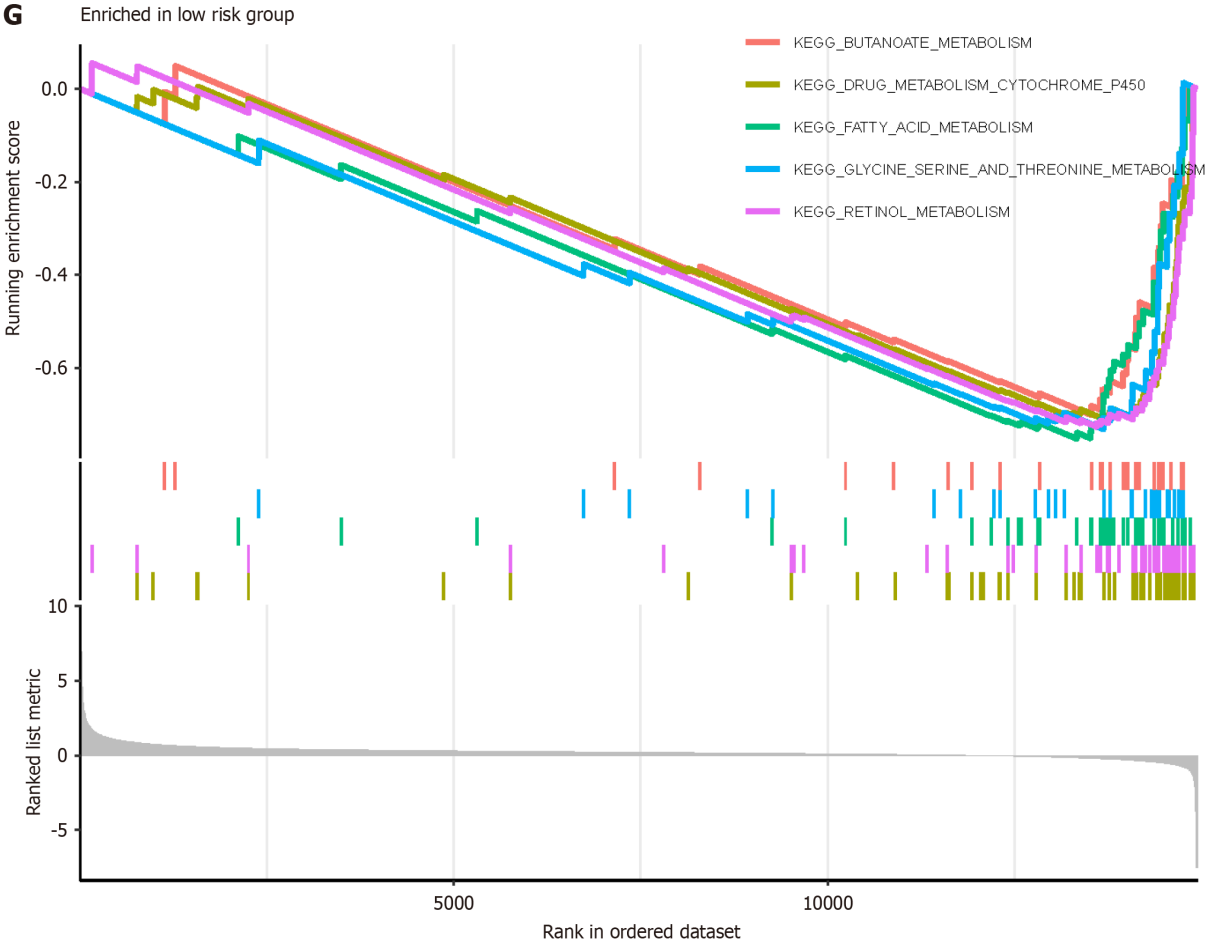

E
Extracellular matrix organization
Extracellular structure organization
External encapsulating structure organization
Response to decreased oxygen levels
Regulation of Wnt signaling pathway
Response to hypoxia
Multi-organism reproductive process
Multi-multicellular organism process
Female pregnancy
Extracellular matrix disassembly
Apical part of cell
Apical plasma membrane
Collagen-containing extracellular matrix
Basal part of cell
Basal plasma membrane
Cell projection membrane
Basolateral plasma membrane
Microvillus
Photoreceptor inner segment
Tertiary granule lumen
G protein-coupled receptor binding
Glycosaminoglycan binding
Organic anion transmembrane transporter activity
Extracellular matrix structural constituent
Collagen binding
Monosaccharide binding
Calcium-dependent protein binding
CXCR chemokine receptor binding
Carbohydrate kinase activity
Arachidonic acid epoxygenase activity
BP
CC
MF
0.025
0.050
0.075
GeneRatio
P value
0.005
0.010
0.015
Count
10
20
30


F
Enriched in high risk group
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATH
KEGG_CELL_CYCLE
KEGG_ECM_RECEPTOR_INTERACTION
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM
KEGG_PATHWAYS_IN_CANCER
Running enrichment score
0.6
0.4
0.2
0.0
10
5
0
-5
Ranked list metric
5000
10000
Rank in ordered dataset


G
Enriched in low risk group
KEGG_BUTANOATE_METABOLISM
KEGG_DRUG_METABOLISM_CYTOCHROME_P450
KEGG_FATTY_ACID_METABOLISM
KEGG_GLYCINE_SERINE_AND_THREONINE_METABOLISM
KEGG_RETINOL_METABOLISM
Running enrichment score
0.0
-0.2
-0.4
-0.6
10
5
0
-5
Ranked list metric
5000
10000
Rank in ordered dataset

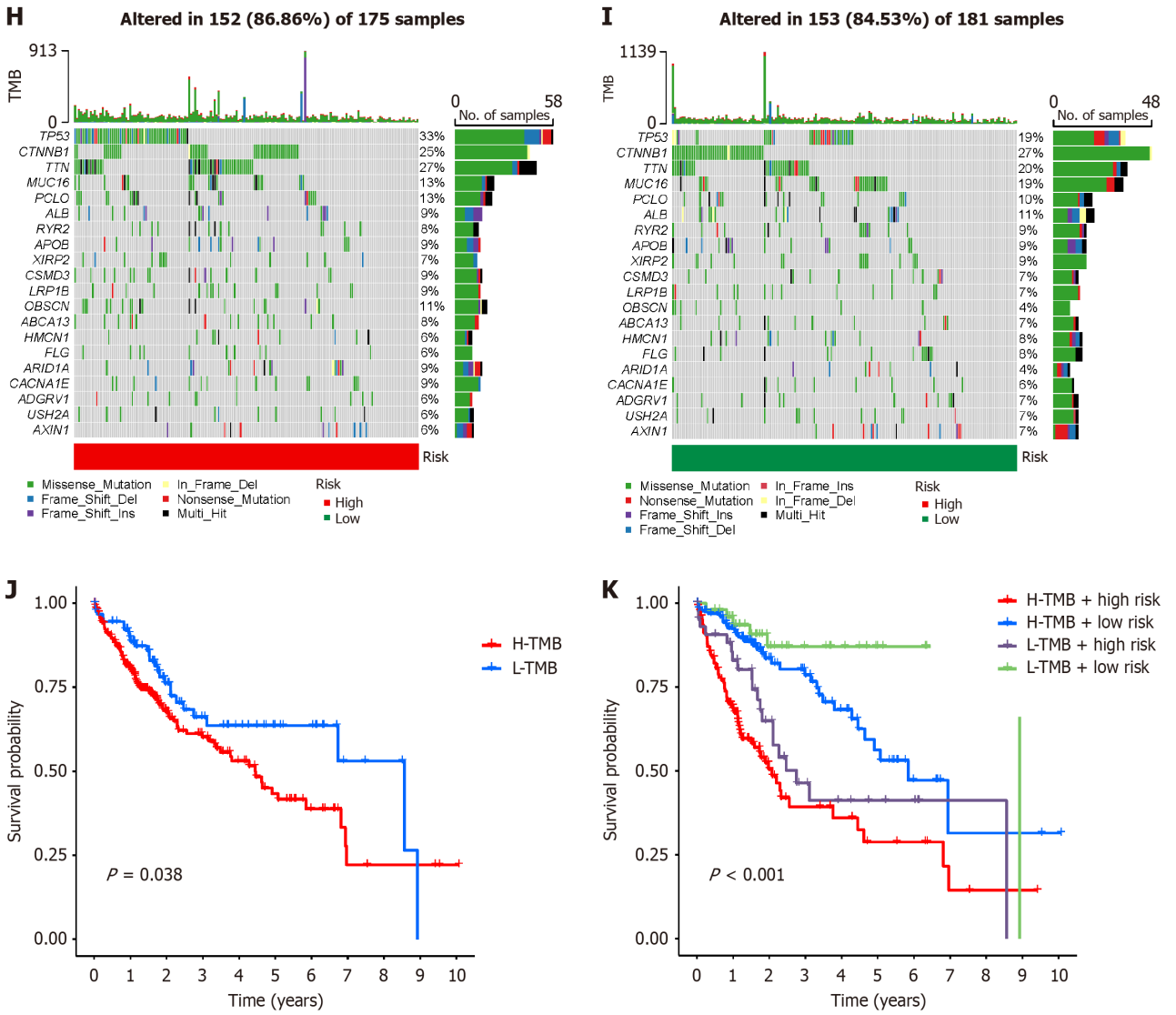
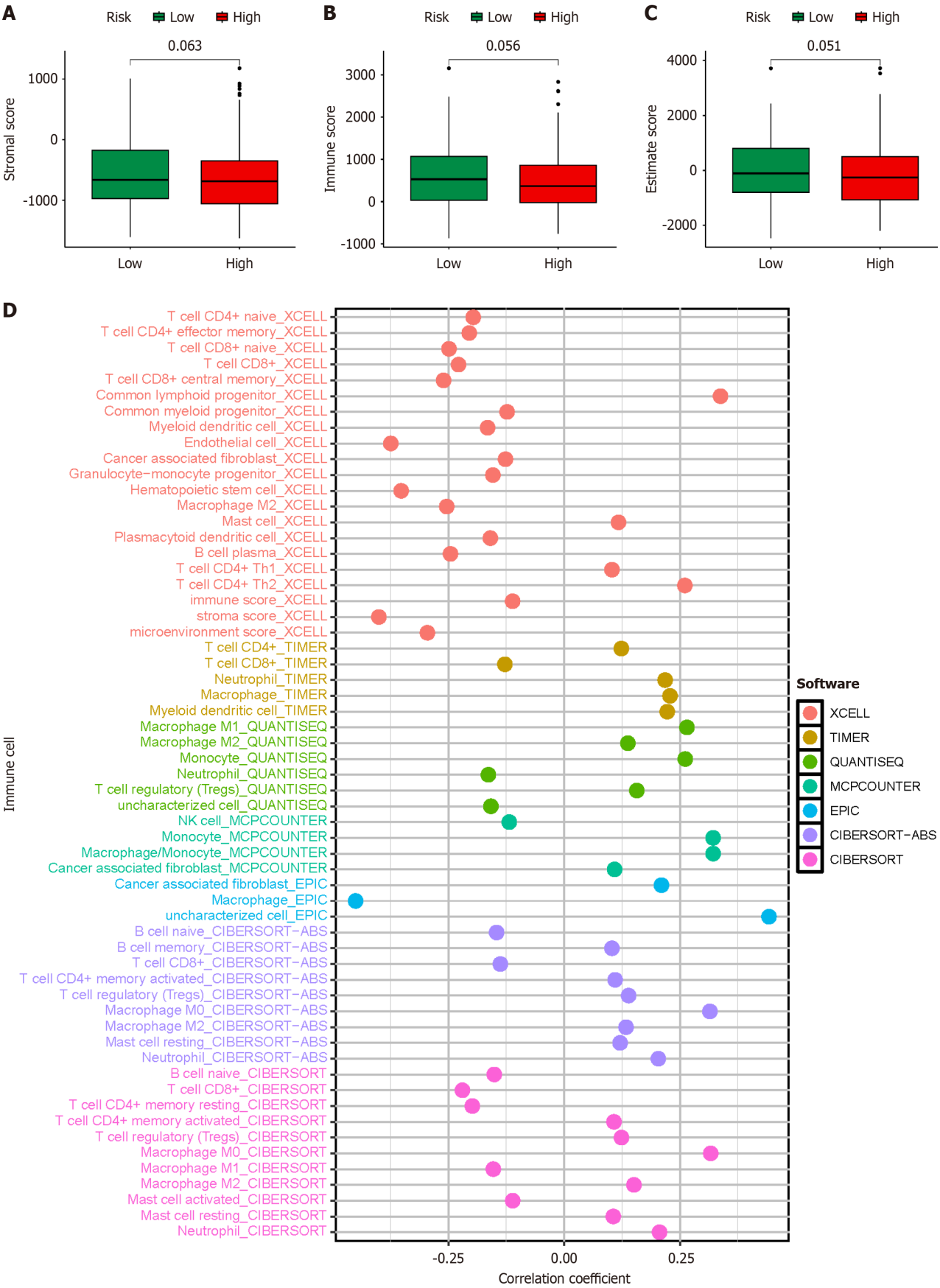


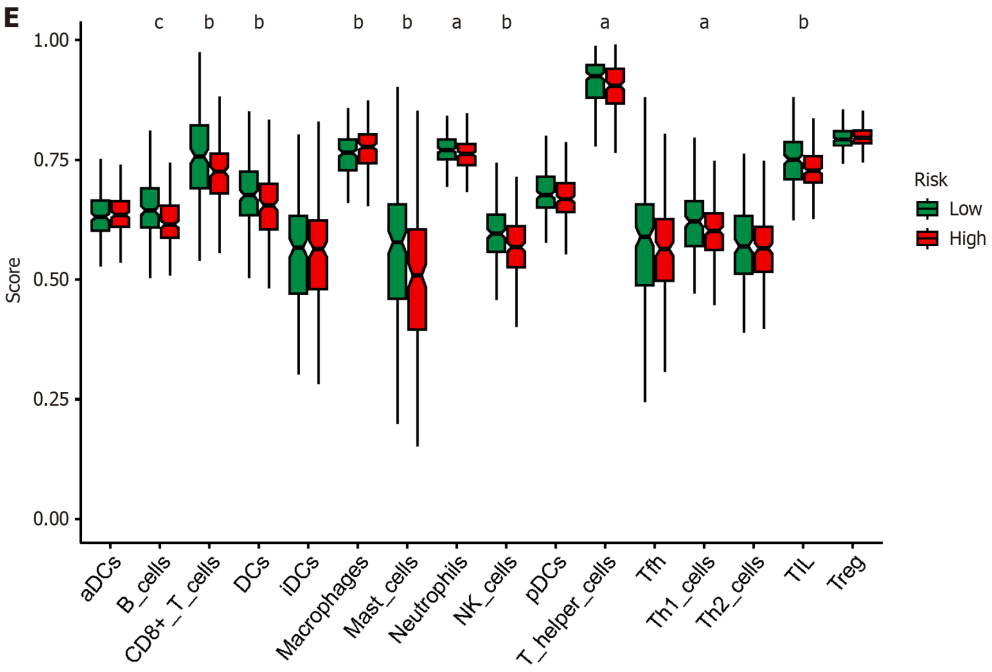
Figure 7 Functional enrichment analysis of different risk score groups. A: Heatmap displays the expression levels of the top 50 differentially expressed genes across different risk score groups in hepatocellular carcinoma (HCC) samples; B: Volcano plot illustrates the differentially expressed genes across different risk score groups. Red indicates fold change > 2, false discovery rate (FDR) < 0.05; green indicates fold change < 2, FDR < 0.05; C: Bubble plot presents the Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis results across different risk score groups; D: Bubble plot demonstrates gene ontology (GO) enrichment analysis pathways and proportions across different risk score groups; E: Bubble plot exhibits GO enrichment analysis pathways, number of genes, and their statistical significance across different risk score groups; F: Gene set enrichment analysis (GSEA) analysis reveals the key pathways enriched in HCC patients with high risk scores; G: GSEA analysis unveils the key pathways enriched in HCC patients with low risk scores; H: Somatic mutation data analysis showcases the mutation rates of key genes in HCC patients with high risk scores; I: Somatic mutation data analysis displays the mutation rates of key genes in HCC patients with low risk scores; J: Survival analysis illustrates the prognosis of HCC patients in different tumor mutation burden groups; K: Survival analysis demonstrates the impact of tumor mutation burden combined with risk score groups on the prognosis of HCC patients. FC: Fold change; ECM: Extracellular matrix; HIF: Hypoxia-inducible factor; KEGG: Kyoto encyclopedia of genes and genomes.

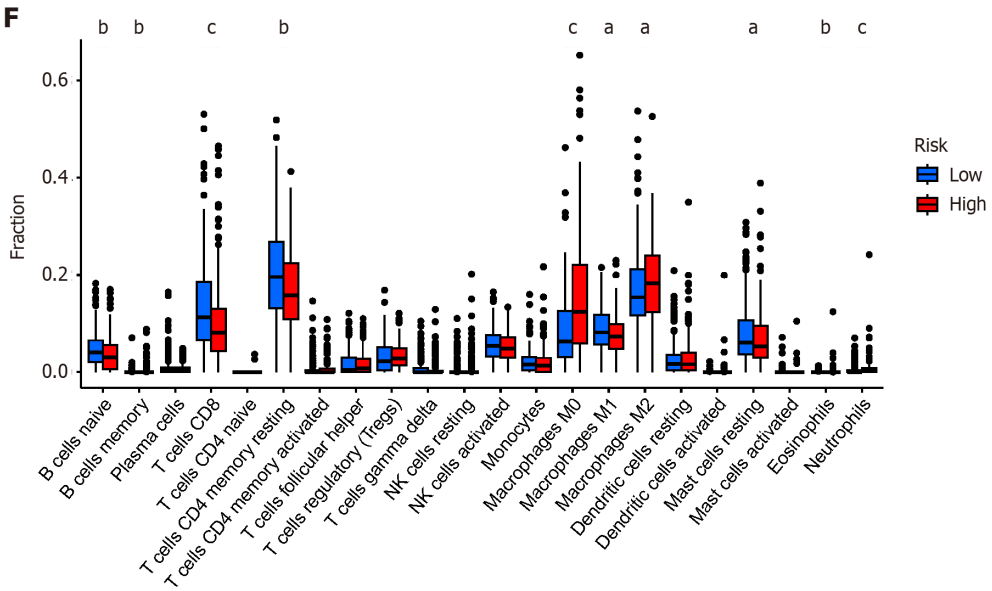
immunotherapy in the IMvigor210 immune treatment cohort using the BRGs prognosis model and found that high-risk patients showed significantly poor response to immunotherapy (Figure 8K). This suggests that high-risk group patients may require alternative therapeutic agents to improve efficacy. Therefore, based on drug sensitivity analysis, we have identified potential targeted drugs such as osimertinib, gefitinib, GDC0810, and paclitaxel (Supplementary Figure 1) that may be beneficial for high-risk group patients. These drugs, in combination with immunotherapy, could serve as future references for further validation in clinical experiments.

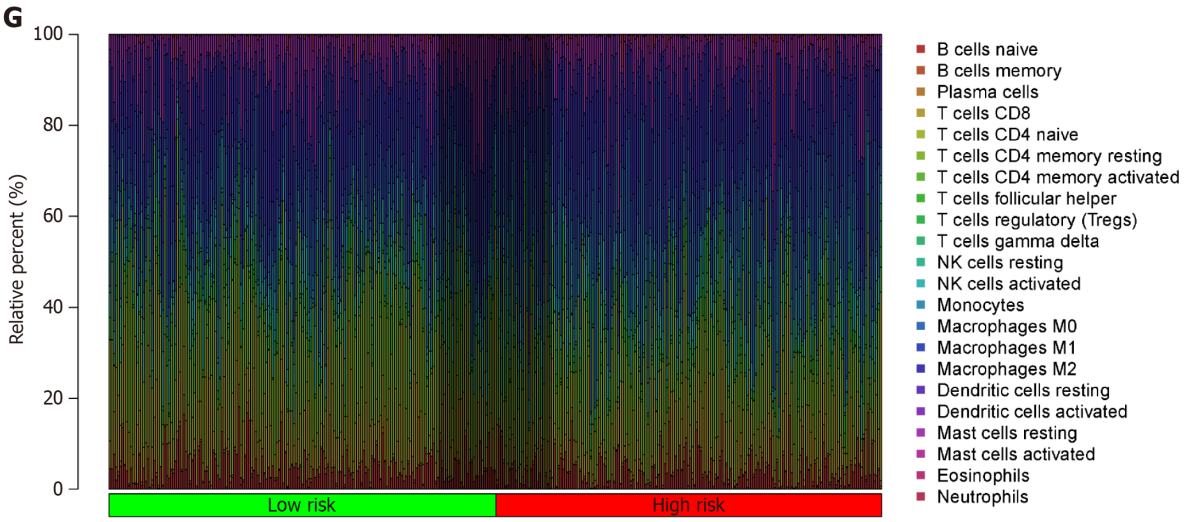
Novel HCC molecular classification based on 11 BRGs

Current immunotherapy for HCC patients yields only a 15%–30% remission rate, possibly due to inadequate differentiation among patients with distinct immune microenvironments, thus failing to achieve personalized precision treatment. Therefore, identifying novel molecular subtyping for HCC is imperative[7]. Leveraging all 11 BRGs in the prognosis model, we classified HCC patients into molecular subtypes using consensus cluster plus. Based on delta area and CDF curves, we observed good stability in sample clustering when k = 3 (Figure 9A and B). We depicted sample distribution under different k values (Figure 9C). A heatmap of CM demonstrated consistent blue shading when k = 3


A
Risk Low High
0.063
Stromal score
1000
0
-1000
Low
High
B
Risk Low High
0.056
Immune score
3000
2000
1000
0
-1000
Low
High
C
Risk Low High
0.051
Estimate score
4000
2000
0
-2000
Low
High
D
T cell CD4+ naive_XCELL
T cell CD4+ effector memory_XCELL
T cell CD8+ naive_XCELL
T cell CD8+_XCELL
T cell CD8+ central memory_XCELL
Common lymphoid progenitor_XCELL
Common myeloid progenitor_XCELL
Myeloid dendritic cell_XCELL
Endothelial cell_XCELL
Cancer associated fibroblast_XCELL
Granulocyte−monocyte progenitor_XCELL
Hematopoietic stem cell_XCELL
Macrophage M2_XCELL
Mast cell_XCELL
Plasmacytoid dendritic cell_XCELL
B cell plasma_XCELL
T cell CD4+ Th1_XCELL
T cell CD4+ Th2_XCELL
immune score_XCELL
stroma score_XCELL
microenvironment score_XCELL
T cell CD4+_TIMER
T cell CD8+_TIMER
Neutrophil_TIMER
Macrophage_TIMER
Myeloid dendritic cell_TIMER
Macrophage M1_QUANTISEQ
Macrophage M2_QUANTISEQ
Monocyte_QUANTISEQ
Neutrophil_QUANTISEQ
T cell regulatory (Tregs)_QUANTISEQ
uncharacterized cell_QUANTISEQ
NK cell_MCPCOUNTER
Monocyte_MCPCOUNTER
Macrophage/Monocyte_MCPCOUNTER
Cancer associated fibroblast_MCPCOUNTER
Cancer associated fibroblast_EPIC
Macrophage_EPIC
uncharacterized cell_EPIC
B cell naive_CIBERSORT−ABS
B cell memory_CIBERSORT−ABS
T cell CD8+_CIBERSORT−ABS
T cell CD4+ memory activated_CIBERSORT−ABS
T cell regulatory (Tregs)_CIBERSORT−ABS
Macrophage M0_CIBERSORT−ABS
Macrophage M2_CIBERSORT−ABS
Mast cell resting_CIBERSORT−ABS
Neutrophil_CIBERSORT−ABS
B cell naive_CIBERSORT
T cell CD8+_CIBERSORT
T cell CD4+ memory resting_CIBERSORT
T cell CD4+ memory activated_CIBERSORT
T cell regulatory (Tregs)_CIBERSORT
Macrophage M0_CIBERSORT
Macrophage M1_CIBERSORT
Macrophage M2_CIBERSORT
Mast cell activated_CIBERSORT
Mast cell resting_CIBERSORT
Neutrophil_CIBERSORT
Immune cell
-0.25
0.00
0.25
Correlation coefficient
Software
XCELL
TIMER
QUANTISEQ
MCPCOUNTER
EPIC
CIBERSORT−ABS
CIBERSORT


E
c b b b b a b a a b
1.00
0.75
0.50
0.25
0.00
Score
aDCs
B_cells
CD8+_T_cells
DCs
iDCs
Macrophages
Mast_cells
Neutrophils
NK_cells
pDCs
T_helper_cells
Tfh
Th1_cells
Th2_cells
TIL
Treg
Risk
Low
High


F
b b c b c a a a b c
0.6
0.4
0.2
0.0
Fraction
B cells naive
B cells memory
Plasma cells
T cells CD8
T cells CD4 naive
T cells CD4 memory resting
T cells CD4 memory activated
T cells follicular helper
T cells regulatory (Tregs)
T cells gamma delta
NK cells resting
NK cells activated
Monocytes
Macrophages M0
Macrophages M1
Macrophages M2
Dendritic cells resting
Dendritic cells activated
Mast cells resting
Mast cells activated
Eosinophils
Neutrophils
Risk
Low
High


G
100
80
60
40
20
0
Relative percent (%)
Low risk
High risk
B cells naive
B cells memory
Plasma cells
T cells CD8
T cells CD4 naive
T cells CD4 memory resting
T cells CD4 memory activated
T cells follicular helper
T cells regulatory (Tregs)
T cells gamma delta
NK cells resting
NK cells activated
Monocytes
Macrophages M0
Macrophages M1
Macrophages M2
Dendritic cells resting
Dendritic cells activated
Mast cells resting
Mast cells activated
Eosinophils
Neutrophils

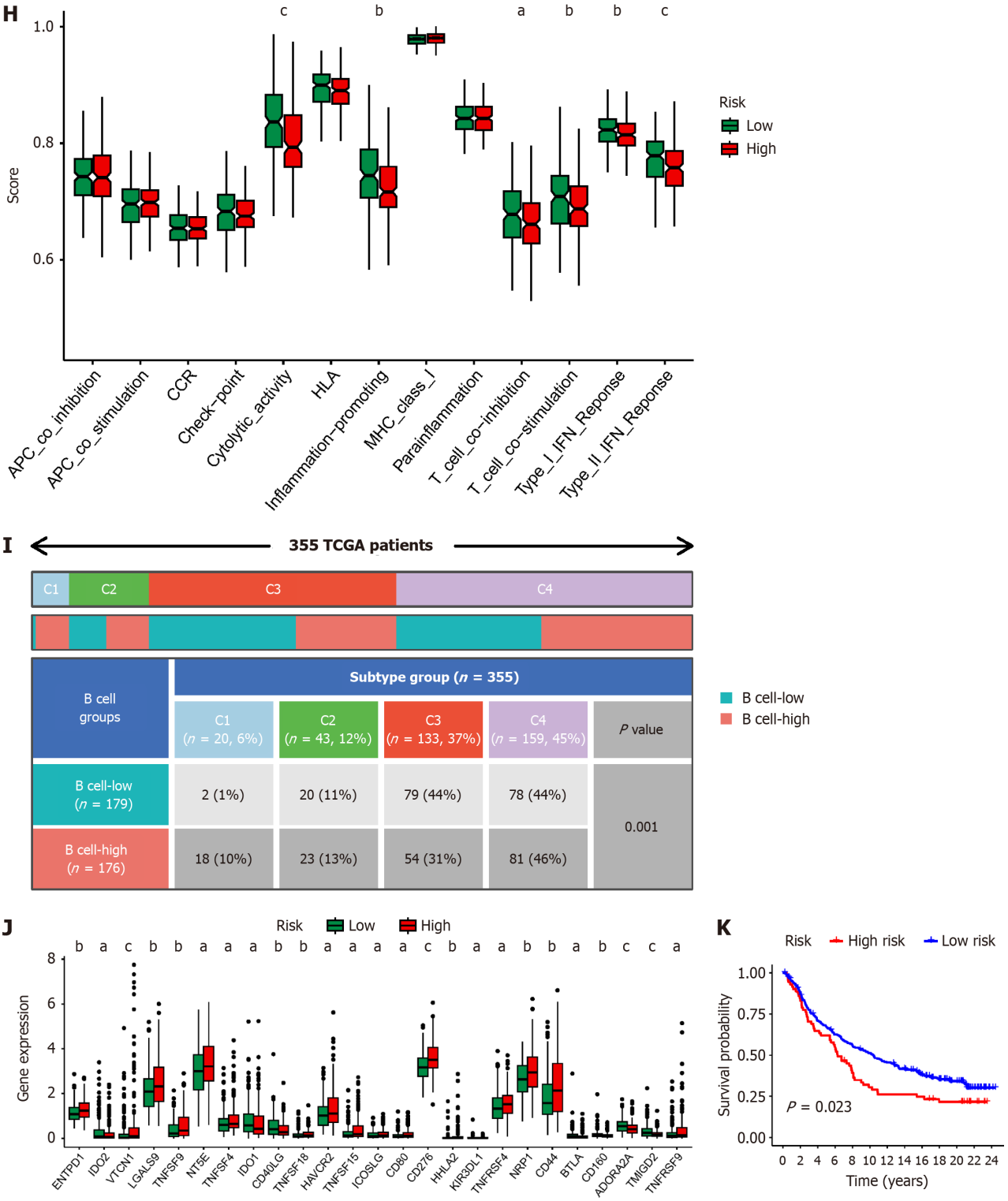
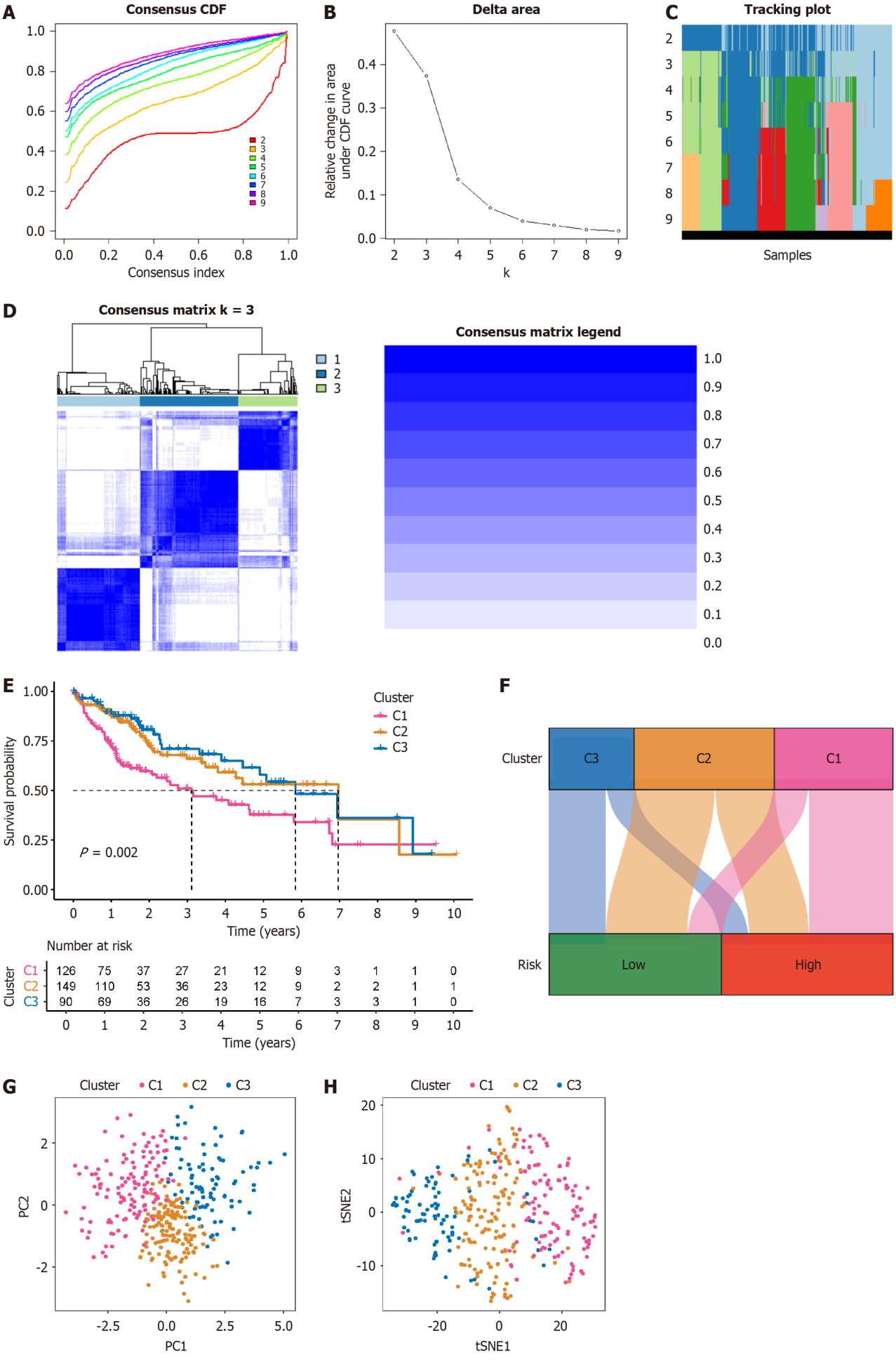


Figure 8 Assessment of the immune microenvironment in different risk score groups. A: Box plot illustrates the stromal score across different risk score groups; B: Box plot displays the immune score across different risk score groups; C: Box plot showcases the estimate score across different risk score groups; D: Bubble plot demonstrates the correlation between risk score and immune cell infiltration within hepatocellular carcinoma samples; E: Box plot shows the abundance of immune cells across different risk score groups calculated based on the single-sample gene set enrichment analysis (ssGSEA) algorithm; F: Box plot exhibits the abundance of immune cells across different risk score groups calculated based on the cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT) algorithm; G: Heatmap displays the distribution and proportions of immune cells across different risk score groups calculated based on the CIBERSORT algorithm; H: Box plot demonstrates the immune functional status across different risk score groups calculated based on the ssGSEA algorithm; I: Association between The Cancer Genome Atlas immune subtypes and BRGs prognostic subtypes; J: Box plot showcases the expression of immune checkpoint genes across different risk score groups; K: Survival analysis depicts the immune therapy response and efficacy in different risk score groups of the IMvigor210 immune therapy cohort. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$. LIHC: Liver hepatocellular carcinoma; CD: Cluster of differentiation; NK: Nature kill; DC: Dendritic cells; HLA: Human leukocyte antigen; TCGA: The cancer genome atlas.


A
Consensus CDF
Consensus index
B
Delta area
Relative change in area under CDF curve
k
C
Tracking plot
Samples
D
Consensus matrix k = 3
Consensus matrix legend
E
Survival probability
P = 0.002
Time (years)
Cluster
C1
C2
C3
Number at risk
C1 126 75 37 27 21 12 9 3 1 1 0
C2 149 110 53 36 23 12 9 2 2 1 1
C3 90 69 36 26 19 16 7 3 3 1 0
F
Cluster
Risk
Low
High
G
PC1
PC2
H
tSNE1
tSNE2

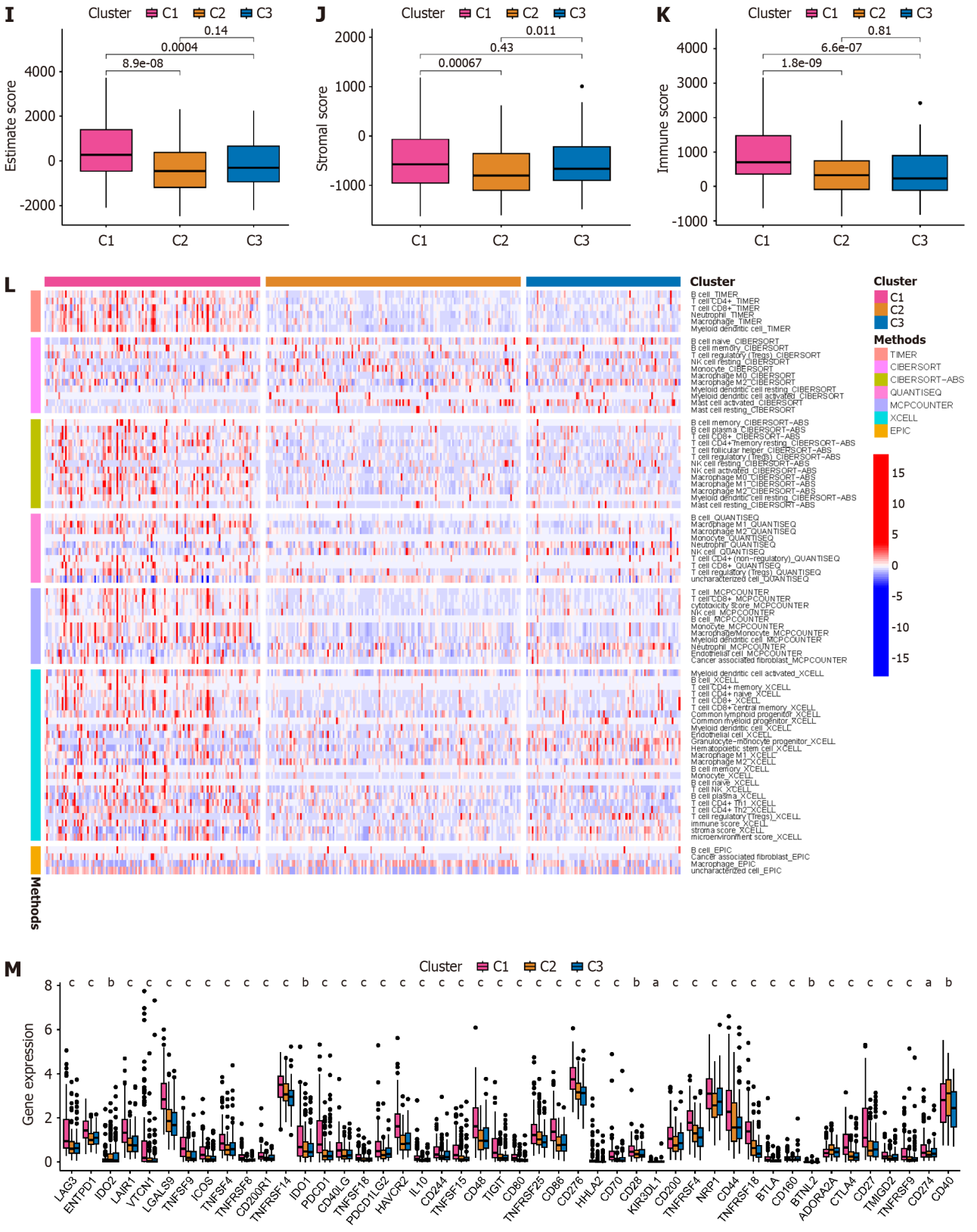


Figure 9 Novel molecular subtyping for identification of hepatocellular carcinoma based on B-cell-related genes. A: Cumulative distribution function curves for different numbers of classifications, where different curves represent the stability of models at different *k* values; B: Distribution of samples across different numbers of classifications; C: Heatmap displays distribution of hepatocellular carcinoma (HCC) patients under different *k* values; D: Consistency clustering plot displays the clustering results when *k* = 3; E: Survival curves illustrate the prognosis of HCC patients with different molecular subtypes; F: Sankey diagram shows the correspondence between different molecular subtypes of HCC patients and different risk score groups; G: Principal component analysis shows the distribution of samples across different HCC molecular subtypes; H: T-distributed stochastic neighbor embedding analysis shows the distribution of samples across different HCC molecular subtypes; I: Box plot demonstrates the estimate score across different HCC molecular subtypes; J: Box plot showcases the stromal score across different HCC molecular subtypes; K: Box plot displays the immune score across different HCC molecular subtypes; L: Heatmap displays the immune cell infiltration status

across different HCC molecular subtypes based on different algorithms; M: Box plot demonstrates the expression of immune checkpoint genes across different HCC molecular subtypes. [a]*P* < 0.05; [b]*P* < 0.01; [c]*P* < 0.001.

(Figure 9D). Subsequently, the C1 group had the poorest prognosis, while those in the C2 and C3 groups exhibited better prognosis based on survival analysis (Figure 9E). A Sankey diagram illustrated the correspondence between novel molecular subtyping and prognosis model grouping (Figure 9F). PCA and t-distributed stochastic neighbor embedding analyses both distinguished HCC patients based on the novel molecular subtyping (Figure 9G and H). We attempted to ascertain whether the novel molecular subtyping could differentiate HCC patients with distinct immune features. Analysis of the immune microenvironment indicated that patients in the C1 group had high estimate scores, stromal scores, and immune scores, whereas those in the C2 group had low scores, with C3 group patients falling between the two (Figure 9I–K). Regarding immune cell infiltration, C1 group patients exhibited markedly elevated levels across various immune cell types, possibly contributing to their poorer prognosis due to immune resource depletion, whereas C2 and C3 group patients showed low levels of immune cell infiltration (Figure 9L). Immune checkpoint analysis revealed significant upregulation of most immune checkpoint genes (42 of 46) in C1 group patients, indicating their potential benefit from immune checkpoint inhibitors. C2 patients might benefit from *CD40* inhibitors, while C3 patients might benefit from *IDO2*, *KIR3DL1*, and *CD160* inhibitors (Figure 9M). We analyzed potential targeted drugs suitable for HCC patients in each immune subtype. C1 group patients were most likely to benefit from staurosporine, pevonedistat, and midkine (MK)-8776, while C2 group patients might benefit from podophyllotoxin bromide and elephantin, and C3 group patients might benefit from epirubicin, extracellular regulated protein kinases (ERK)-2440, and Janus kinase (JAK)-8517 (Supplementary Figure 2).

DISCUSSION

Although the role of T cells in antitumor immunity has been extensively studied, the role of B cells, including in HCC, remains poorly understood, hindering efforts to utilize B-cell responses for cancer immunotherapy[24]. B cells, as a crucial subset of antigen-presenting cells, play a significant role, which is often overlooked in tumor immunotherapy, including HCC. Unlike dendritic cells and macrophages, which primarily present antigens through phagocytosis, B cells predominantly present antigens through the high-affinity binding of the B-cell receptor (BCR) to the antigen, thereby effectively recognizing low levels of antigens and enhancing antigen presentation efficiency. Upon binding of antigens to specific BCRs, the process of antigen internalization initiates, and the antigens are displayed on the surface of B cells *via* MHC class II molecules, activating cognate $CD4^+$ helper T cells, thus inducing antibody production[25]. Based on gene enrichment analysis of BRGs, B cells and T cells (including $CD4^+$ and $CD8^+$ T cells) significantly enrich pathways associated with HCC occurrence and development, such as T-cell receptor signaling pathway and natural-killer-cell mediated cytotoxicity. B cells and T cells jointly regulate important biological processes such as GO nuclear transcribed mRNA catabolic process nonsense mediated decay and GO translational elongation. Our analysis reveals a potential synergistic interaction between B cells and T cells in HCC. Our findings suggest that B cells play a crucial role in activating $CD4^+$ T cells and may act in conjunction with $CD8^+$ T cells. This discovery represents a novel breakthrough in tumor therapy.

The role of B cells in most tumors, including HCC, remains a subject of considerable controversy[25]. Among the 11 key genes in our BRGs prognostic model, *BLNK* is associated with a favorable prognosis in HCC, exhibiting high expression in B cells within HCC. Conversely, *CALM1*, *LEPROTL1*, *S100A10*, *LDHA*, *LYAR*, *CKLF*, and *TXN* are linked to an adverse prognosis in HCC, displaying low expression in B cells within HCC. The alignment of these BRGs with the prognostic outcomes of HCC, as reflected in their expression within B cells, suggests that B-cell activation is a favorable prognostic factor for HCC. However, certain BRGs exhibit discrepancies between their overall expression in HCC and their expression specifically within B cells. For instance, *FYN* and *KLRB1* are associated with a favorable prognosis in HCC but demonstrate low expression in B cells within HCC, while *MARCKSL1* is linked to an adverse prognosis in HCC yet exhibits high expression in B cells within HCC. These findings suggest potential complexities in the roles of these BRGs, indicating that their functions may extend beyond B cells, warranting further investigation. The high risk score group identified by the BRGs prognostic model shows significant enrichment in pathways such as ECM–receptor interaction, central carbon metabolism in cancer, protein digestion and absorption, HIF-1 signaling pathway, biosynthesis of amino acids, and fructose and mannose metabolism. This implies that B cells may regulate the occurrence and progression of HCC through these pathways, necessitating further validation in future studies.

Similar to regulatory T cells, B cells can also exhibit regulatory phenotypes to suppress immune responses. They express inhibitory receptors on their surface, akin to immune checkpoint genes. These include a variety of immune checkpoint molecules like programmed cell death protein 1 (PD-1) and its ligands PD ligand 1 (PD-L1)/PD ligand 2, which play diverse regulatory roles in both humoral and cellular immunity[26]. Recent findings in HCC reveal that B cells with elevated PD-1 expression, when encountering PD-L1-expressing cells, induce T-cell suppression by releasing interleukin-10. Blocking PD-1 on B cells with checkpoint blockade antibodies has shown promise in enhancing cancer immunotherapy[27]. Anti-PD-1 therapy has become the preferred immunotherapy for treating HCC. However, anti-PD1 therapy targeting T cells has only achieved a 15% response rate in HCC patients[7]. In this context, anti-PD-1 therapy targeting B cells may potentially become an important approach to improving the efficacy of immunotherapy for HCC patients. Our results indicate significant upregulation in expression of most T-cell immune checkpoint genes in the high

risk scoring group of HCC patients, with *ENTPD1*, *NT5E*, and *HAVCR2* being among the immune checkpoint genes highly expressed in B cells[23]. Targeting inhibitors against these shared immune checkpoint genes in both B cells and T cells may effectively harness the synergistic action of these cells in HCC therapy; a hypothesis deserving validation in future multicenter large-scale clinical trials.

Our prognostic model for HCC, termed BRGs, offers guidance in diagnosis and prognosis prediction. Through univariate Cox regression and LASSO regression analysis, we constructed the BRGs prognostic model. Our analysis indicates a significant reduction in overall survival for patients in the high-risk group compared to those in the low-risk group. Furthermore, through visualizations such as risk curves, risk heatmaps, ROC curves, and Kaplan–Meier survival curves, we validated the robust predictive power of our risk model, which outperformed other significant risk factors in HCC such as age, grade, and stage. Importantly, similar robust results were replicated in two external validation sets for HCC (ICGC and GSE76427), bolstering the reliability and reproducibility of our research findings.

Beyond elucidating the role of B cells in HCC, identifying precise molecular subtypes is crucial for enhancing personalized treatment, given the widespread resistance of HCC to targeted therapies[28]. Leveraging 11 BRGs from our prognostic model, we classified HCC patients into three molecular subtypes. Our results indicate that C1 patients exhibited the most extensive immune cell infiltration, potentially indicating immune exhaustion and consequently the poorest prognosis. However, these patients may benefit from targeted drugs such as staurosporine, pevonedistat, and MK-8776. Conversely, C2 and C3 patients showed better prognosis. C2 patients may improve their prognosis with drugs such as podophyllotoxin bromide and elephantin, while C3 patients may benefit from drugs such as epirubicin, ERK-2440, and JAK-8517. Our proposed novel HCC molecular subtypes hold significant implications for precise HCC treatment.

CONCLUSION

Our research suggests that in HCC, B cells play a role in tumor cytotoxicity by activating $CD4^+$ and $CD8^+$ T cells. We have established a reliable BRGs prognostic model and novel molecular subtypes, offering pivotal and valuable references for the diagnosis, prognosis, and personalized treatment strategies of HCC.

FOOTNOTES

Author contributions: Xu KQ, Gong Z and Chen X designed the research; Xu KQ and Gong Z performed the research; Yang JL, Xia CQ and Zhao JY contributed new reagents or analytic tools; Xu KQ, Gong Z and Chen X analyzed the data; Xu KQ, Gong Z and Chen X wrote the paper; All authors contributed to the study design, interpretation of the investigations, data analysis, and manuscript review; Xu KQ and Gong Z are listed as co-first authors because they made equal and significant contributions throughout the research process, being jointly responsible for key aspects such as experimental design and data analysis; Chen X is designated as corresponding author due to his crucial roles in the research design and experimental processes, overseeing the entire study's planning and supervision, as well as being responsible for interpreting the data and publishing the results; In summary, the authorship order reflects their actual contributions and roles in the research.

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LETTER TO THE EDITOR

Recent progress of gastroesophageal reflux after endoscopic myotomy

Xuan Yan, Wei-Hong Sha

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Abstract

Per-oral endoscopic myotomy (POEM) is an innovative minimally invasive technique and has emerged as the preferred modality for treating achalasia and spastic esophageal disorders in numerous specialized centers worldwide. Gastroesophageal reflux (GER) is a common complication following POEM procedures. Recently, an article in the *World Journal of Gastroenterology*, providing a comprehensive update on post-POEM GER. In this article, the authors present novel insights and strategies that offer valuable implications for endoscopy.

Key Words: Per-oral endoscopic myotomy; Gastroesophageal reflux; Progress; Treatment; Update

Core Tip: The article highlighted the significance of predictive methods in identifying patients at risk of developing gastroesophageal reflux (GER) following per-oral endoscopic myotomy (POEM) surgery. By evaluating novel technologies and refined clinical indicators, clinicians could anticipate the likelihood of postoperative reflux and tailor treatment strategies accordingly. Overall, the core tip of the article served as a comprehensive guide for clinicians involved in the management of patients undergoing POEM procedures. By emphasizing the importance of predictive, preventive, and management strategies, the article aimed to enhance treatment outcomes, reduce complications, and optimize patient care standards in the context of post-POEM GER.

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TO THE EDITOR

Achalasia is a rare esophageal motility disorder characterized by the loss of peristalsis and inadequate relaxation of the lower esophageal sphincter, particularly during swallowing[1-3]. Treatment options aim to improve the passage of food through the gastroesophageal junction and include standard therapies such as botulinum toxin injection, pneumatic balloon dilation, laparoscopic Heller myotomy, and newer treatment modalities such as per-oral endoscopic myotomy (POEM)[4]. The article "Prediction, prevention and management of gastroesophageal reflux after per-oral endoscopic myotomy: An update" published in the *World Journal of Gastroenterology*[1], provides a comprehensive review of the latest advances in the prediction, prevention, and management of gastroesophageal reflux (GER) following POEM. The study highlighted significant improvements in prediction methods, including the introduction of novel technologies and clinical indicators. Furthermore, it explored various preventive strategies aimed at reducing the incidence of post-POEM GER, such as advancements in preoperative preparation and postoperative management. Additionally, the article outlined updated treatment methods, offering insights into new treatment modalities and surgical interventions for addressing reflux symptoms post-POEM. These findings are pivotal as they contribute to enhancing treatment outcomes, reducing complication rates, and help physicians optimize patient care. Overall, this study sheds light on the evolving landscape of GER management post-POEM, with potential implications for clinical practice and patient care.

POEM is a minimally invasive surgical technique used to treat achalasia, a condition characterized by impaired esophageal motility. During POEM, an endoscope is inserted through the mouth and into the esophagus, where a myotomy, or surgical incision, is made in the inner lining of the esophagus to relieve the obstruction caused by dysfunctional lower esophageal sphincter muscles. While POEM effectively alleviates symptoms of achalasia, such as dysphagia, it has been associated with an increased risk of postoperative GER. This reflux can lead to complications such as esophagitis, Barrett's esophagus, and even esophageal adenocarcinoma if left untreated. Therefore, understanding and managing GER after POEM is crucial for optimizing patient outcomes and preventing long-term complications. The clinical significance of addressing post-POEM GER lies in ensuring the success and safety of this therapeutic intervention for patients with achalasia.

In their comprehensive review titled "Prediction, prevention and management of GER after per-oral endoscopic myotomy: An update", Nabi *et al*[1] assessed the strategic interventions aimed at addressing GER following POEM. The authors emphasized the urgent need for advanced methods to predict the occurrence of post-POEM GER. These predictive methods incorporated cutting-edge technologies and refined clinical indicators, providing clinicians with valuable insights to anticipate and preempt potential reflux complications. Moreover, the study underscored the significance of implementing multifaceted preventive strategies to mitigate the incidence of post-POEM GER. Enhanced preoperative assessments, tailored patient selection criteria, and meticulous intraoperative techniques are advocated to minimize disruptions to esophageal anatomy and optimize surgical outcomes. The meticulous attention to detail in these preoperative and intraoperative phases aimed to reduce the risk of GER-related complications, thereby enhancing patient safety and satisfaction. In addition, the authors discussed comprehensive postoperative management protocols aimed at effectively reducing GER-related complications and optimizing long-term outcomes for patients undergoing POEM. These management strategies include close monitoring of symptoms, timely pharmacologic interventions, and judicious dietary changes. By addressing GER symptoms promptly and proactively, clinicians can minimize the risk of complications and improve overall patient outcomes[5]. In response to these findings, the authors advocated for the use of a dual-scope technique to precisely control the length of the gastric myotomy. This refined surgical approach not only assists in determining the optimal myotomy length but also facilitates the assessment of myotomy direction, thereby reducing the likelihood of reflux-related complications[6]. In addition, studies have shown that patients who retain sling fibers post-POEM have a significantly lower incidence of grade B or higher reflux esophagitis than those who do not (31.3% *vs* 58.1%)[7]. Although the overall incidence of reflux esophagitis was similar between the conventional group and the sling fiber retention group, the latter group exhibited a significantly lower frequency of severe esophagitis (Los Angeles grade C/D) (44.1% *vs* 18.5%)[8]. Furthermore, the study suggested that post-POEM reflux esophagitis responds well to proton pump inhibitors, with refractory GER disease being significantly less common after POEM. These findings highlighted the importance of proactive management strategies in mitigating GER-related complications and optimizing long-term outcomes for patients undergoing POEM[9]. In summary, the meticulous exploration of predictive, preventive, and management strategies in this study offered valuable insights into the evolving landscape of GER management post-POEM. By advocating for refined surgical techniques and comprehensive management protocols, the authors aimed to empower clinicians to make informed decisions and enhance patient care standards in this specialized domain.

In conclusion, the study by Nabi *et al*[1] provides a comprehensive update on post-POEM GER, offering new insights and strategies for clinical practice. Future research endeavors are anticipated to further refine management strategies in this field, contributing to the health and well-being of patients.

FOOTNOTES

Author contributions: Yan X and Sha WH designed the research study; Yan X and Sha WH performed the research.

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LETTER TO THE EDITOR

Real-world clinical efficacy of tofacitinib in moderate-to-severe ulcerative colitis

Sara R Lopes, Claudio Martins, Madalena Teixeira, David Tomás

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

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Abstract

Tofacitinib is an oral small-molecule Janus kinase (JAK) inhibitor that preferentially inhibits JAK1 and JAK3. Its efficacy in inducing and maintaining remission in ulcerative colitis (UC) as well as its safety profile has been demonstrated in multicenter, randomized, double-blind, placebo-controlled trials. Additionally, real-world studies evaluating the effectiveness and adverse effects of tofacitinib have been conducted, affirming its clinical efficacy in moderate-to-severe UC.

Key Words: Ulcerative colitis; Tofacitinib; Real-world studies; Inflammatory bowel disease; Janus kinase inhibitor

Core Tip: Tofacitinib, an oral small-molecule agent, has proven efficacy in inducing and maintaining remission among patients with moderate-to-severe ulcerative colitis. Real-world studies have showcased its effectiveness and safety profile to treat ulcerative colitis, primarily within Western countries. There have been a limited number of studies conducted on Asian patients.

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TO THE EDITOR

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by recurrent, relapsing inflammation of the gastrointestinal tract, with a negative effect on quality of life. Symptoms associated with UC include urgency, increased frequency of bowel movements, bloody diarrhea, and abdominal pain[1].

Tofacitinib is an oral, small-molecule Janus kinase (JAK) inhibitor that inhibits all JAKs, but preferentially inhibits JAK1 and JAK3. Efficacy to induce and maintain remission in UC and the safety profile have been proven in multicenter, randomized, double-blind, placebo-controlled trials: OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain [2,3]. Tofacitinib was approved for the treatment of refractory moderate-to-severe UC in 2018. A few real-world studies assessing effectiveness and adverse effects of tofacitinib have been conducted, mainly in Western countries[4-6].

DISCUSSION

With this in mind, we would like to extend our congratulations to Kojima *et al*[7] for their article recently published in the *World Journal of Gastroenterology*. Their results demonstrate the efficacy and safety of tofacitinib for UC in a cohort of Asian patients. In a retrospective unicentric study involving 111 patients with UC, the authors demonstrated that tofacitinib effectively induced and maintained clinical remission. By week 8, 66.3% of UC patients responded to tofacitinib treatment. Although response rates decreased over time, nearly half (47.1%) of the patients still responded in the subsequent weeks. The overall cumulative clinical remission rate at week 48 was 61.7%, and this efficacy was not affected by prior treatment with anti-tumor necrosis factor (TNF)-α agents (P = 0.25). Notably, most patients received prior treatments, with 20.7% (n = 23) using corticosteroids at baseline. These results are consistent with the existing literature. A meta-analysis of 17 studies, including 1162 patients, reported clinical response and remission rates of 62.1% and 34.7% at week 8, respectively[8]. Regarding safety, the authors reported that 34.2% of patients experienced at least one adverse event, leading to treatment discontinuation in 6.3% of cases. The incidence rate of herpes zoster was 7.5 per 100 patient-years, and only one patient developed a thromboembolic complication. The safety profile observed in this study aligns with findings from other real-world studies. The same meta-analysis reported an overall adverse event rate of 26% and an incidence rate of herpes zoster at 6.9 per 100 patient-years[8].

However, the retrospective and unicentric design of the study introduces inherent limitations, including selection bias, potential data inaccuracies, and challenges in controlling confounding variables, along with a limited sample size. Furthermore, there are some unanswered questions that warrant a comment.

Firstly, there is limited data regarding endoscopic healing. Among the 39 patients who underwent endoscopy, the authors reported complete endoscopic remission in 7.7% of patients and an endoscopic remission rate of 23.1% at week 16. Achieving endoscopic remission is a long-term treatment target in UC[9]. While it was not the primary or secondary outcome of this study, it would have been valuable to observe the endoscopic response in more patients and over the extended follow-up period.

Moreover, information about other targets is missing, specifically fecal calprotectin, a recognized intermediate target in UC[9]. As a marker of active disease, it would have been valuable to include this biomarker and observe its trajectory during the follow-up period.

Regarding tapering off treatment after achieving clinical remission, Kojima *et al*[7] found that 45.7% of patients experienced relapse upon tapering off tofacitinib, with most patients (69%) attaining clinical remission at week 12 after re-increasing the dosage. The median duration from the start of tapering to re-escalation of the dosage was 95 days. Analyzing potential disparities in baseline characteristics between patients who experienced relapse and those who did not, particularly in terms of baseline endoscopic findings or prior exposure to TNF-α agents, could offer further insights to aid in identifying individuals at greater risk of relapse.

With respect to safety, while the authors did observe an adverse event rate comparable to that reported in pivotal trials and other real-world studies, the incidence of serious adverse events should be clarified. Serious adverse events encompass not only those necessitating treatment discontinuation, but also those leading to hospitalization, as per standard definitions. Furthermore, concerning the most common adverse event, dyslipidemia, which occurred in 17% of patients, the authors should provide data concerning the fluctuations in serum lipid levels throughout the entire follow-up period, to determine whether these changes are transient or cumulative.

CONCLUSION

Kojima *et al*[7] made a significant contribution by addressing the effectiveness and safety profile of tofacitinib in Asian patients with moderate-to-severe UC. Nonetheless, we agree that prospective longer-term studies, some of which are currently ongoing, are needed to assess predictive factors associated with relapse following the tapering of tofacitinib, and to enhance the management of patients with active UC and concomitant cardiovascular risk factors who are treated with tofacitinib.

FOOTNOTES

Author contributions: Lopes SR and Martins C analyzed the data and wrote the manuscript; All authors have read and approved the final version of the manuscript.

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