Hepatocellular carcinoma (HCC) exerts a heavy disease burden and is currently the second most common cause of cancer-related deaths worldwide. HCC usually lacks obvious symptoms in the early stage, and most HCC patients are diagnosed at advanced stages with poor prognosis. CircULAR RNAs (cirCNAs) are single-stranded RNAs that form covalently closed loops and are stable in exosomes. Exosomes are known as important messengers of the cross-talk between tumor and immune cells. Accumulating studies have demonstrated the promoter or suppressor roles of exosomal circRNAs in the carcinogenesis, progression, and metastasis of HCC. In this review, we summarized the current studies on the biological functions and diagnostic and prognostic values of exosomal circRNAs in HCC progression.

**Keywords:** hepatocellular carcinoma, exosome, circRNAs, metastasis, prognosis

**INTRODUCTION**

Hepatocellular carcinoma (HCC) is the primary malignancy of hepatocytes. Active hepatitis C and B continue to drive most of the global burden of HCC (1, 2). Early-stage HCC can be treated curatively by surgical resection, local ablation, or liver transplantation, and early diagnosis could have a good prognosis with a 5-year survival rate of more than 70% (3, 4). However, HCC usually lacks obvious symptoms in the early stage, and more than 75% of HCC patients are diagnosed at the advanced stage when the tumor is unresectable, making the 5-year survival rate of patients with HCC less than 16% (1, 3). Early detection of HCC is always based on monitoring with ultrasonography and a number of serological markers, namely, alpha-fetoprotein (AFP), Lens culinaris agglutinin-reactive AFP (AFP-L3), Glypican-3, and osteopontin, but their diagnostic accuracies have been shown to be insufficient (5). Therefore, there is an urgent need to explore novel biomarkers for HCC diagnosis.

Circular RNAs (cirCNAs) are single-stranded RNAs that form covalently closed loops (5). Recently, cirCNAs have been recognized as key factors in tumor development and have been found to be abundant and stable in exosomes (6). Exosomes are known as important messengers of the cross-talk between tumor and immune cells (7, 8). CirCNAs may exert their functions via exosomes and tumor stem cells (9). CirCNAs in exosomes provide necessary energy for tumor growth, participate in mutation metabolism in tumors and regulate signal pathways by transporting non-coding RNAs (10). Some evidence indicates that exosomal CirCNAs may contribute to HCC cell proliferation, migration, invasion, and glycolysis by regulating their targeted microRNAs and downstream tumor-related signaling pathways in HCC (11, 12). In this review, we summarized the
current studies on the origin, biological functions, and diagnostic and prognostic value of exosomal circRNAs in HCC progression.

**BIOGENESIS AND FUNCTION OF EXOSOME**

Exosomes are membrane-bound extracellular vesicles (EVs) that originate from the limiting membrane of late endosomes. Exosomes are small, single-membrane, secreted organelles with an average diameter of about 100 nm (13–16). Additionally, exosomes play significant roles in various biological functions, namely, intra- and inter-cellular communication in both physiological and pathological contexts, and the transfer of biomolecules such as proteins, enzymes, lipids, and RNAs in various diseases (17–19). The biogenesis of exosomes begins with the endosome system. After various maturation processes, the nuclear endosomal membrane invaginates to form multivesicular bodies (MVBs). In addition to leading to the generation of intraluminal vesicles (ILVs), MVBs can also fuse with lysosomes for degradation (20). The biogenesis and secretion of exosomes appear to involve several mechanisms. ESCRT-mediated MVB biogenesis is the most extensively described pathway, and it depends on cell type or intracellular homeostasis (20, 21). Some studies pointed out that exosomes were considered promising biomarkers for the diagnosis, treatment, and prognosis of various diseases, especially those that played a key role in the establishment of tumor microenvironment, tumor progression, invasion, metastasis, chemoresistance, and targeted drug delivery (14, 22–26).

**ORIGIN AND FUNCTION OF EXOSOMAL CIRCNRAS**

CircRNAs are a new class of endogenous noncoding RNAs with covalently closed loop structures that lack 5’ caps, 3’ polytails, and polyadenylated tails (27). CircRNAs are evolutionarily conserved, show cell-specific expression patterns, and regulate themselves independently of their linear transcripts (28). The study by Li et al. (29) first reported the existence of abundant exosomal circRNAs, which represented a novel class of stable RNA species in exosomes by RNA-seq analyses. Some studies have discovered that circRNAs are identified in cellular RNAs and can be transferred to exosomes, and subsequently the molecular information is transferred to recipient cells (27, 30).

Exosomes are important mediators of intercellular communication, particularly in the tumor microenvironment (31). Some evidence demonstrated that circRNAs had abundant miRNA binding sites and exerted important biological functions by stabilizing microRNAs (miRNAs), regulating alternative splicing and acting as miRNA inhibitors (‘sponges’), protein ‘decoys’, or by encoding small peptides (31, 32). Tumor cell-derived exosomal circRNAs can act on target cells or organs by the transport of exosomes and play oncogenic or tumor suppressive roles during tumor development (33). With the rise of exosome research, some researchers have investigated the relationship between exosomes and circRNAs in tumors and concluded that circRNAs in exosomes can work as novel biomarkers for tumor diagnosis, thus providing a new development direction for tumor diagnosis (33, 34). Dou et al. (30) found that circRNAs had been detected in cancer-derived exosomes in higher abundance than mutant KRAS cells and suggested a potential involvement of circRNAs in oncogenesis. This finding implied that exosomal circRNAs had the potential as tumor biomarkers. The study by Shang et al. (35) found that circPACRGL was significantly upregulated in colorectal cancer cells (CRC) after tumor-derived exosomes addition and indicated that cancer-derived exosomal circPACRGL played an oncogenic role in CRC proliferation and metastasis. In gastric cancer tissues and serum, the expression of exosomal circSHKBP1 was significantly increased and related to advanced TNM stages and poor prognosis, while exosomal circSHKBP1 regulated the miR-582-3p/HUR/VEGF pathway, suppressed HSP90 degradation, and promoted GC cell proliferation, migration, invasion, and angiogenesis (36). Hsa_circ_0074854 can be transferred from HCC cells to macrophages via exosomes, and the expression of Hsa_circ_0074854 was upregulated. Downregulation of hsa_circ_0074854 can suppress HCC migration and invasion by interacting with HuR and suppressing macrophage M2 polarization (8). Mesenchymal stem cell (MSC)-derived exosomal circular RNAs were a promising treatment for disease. The MSC-derived exosomal circFBXW7 inhibited the proliferation, migration, and invasion of synovial cells and the inflammatory response in rheumatoid arthritis via sponging miR-216a-3p and releasing HDAC4 (37). The study by Preuße et al. (38) found circRNAs were particularly abundant in human platelets compared with other hematopoietic cell types and were packaged and released in both microvesicles and exosomes derived from platelets. Since platelets are associated with hemostasis, inflammation, and cancer metastasis, studies on exosomal circRNAs may provide a novel avenue for many disease diagnoses and therapies (38).

**THE BIOLOGICAL FUNCTIONS OF EXOSOMAL CIRCNRAS IN HCC**

While the exact biological function of most circRNAs in HCC is still largely unknown, the abnormal expressions of exosomal circRNAs were found in tissues, body fluids, and serum/plasma of patients with HCC (39). We summarized the current studies to identify the relationship between exosomal circRNAs and HCC more clearly (shown in Table 1 and Figure 1). Recently, abundant bodies of evidence have revealed the relationship between exosomal circRNAs and HCC progression, namely, proliferation, apoptosis, invasion, metastasis, and glycolysis of HCC cells, resistance mechanisms in HCC therapy, epithelial to mesenchymal transition (EMT) of HCC cells, angiogenesis, recurrence, and mortality, by regulating their targeted miRNAs and downstream tumor-related signaling pathways (41, 46, 47, 51, 55, 59). In Table 1, most of the upregulated circRNAs are positively associated with HCC progression, except for exosomal circ-0072088 and hsa_circ_0004658. Furthermore, hsa_circ_0051443 and hsa_circ_0028861 are downregulated and inhibit HCC progression.
| CircRNAs                                    | Expression | Parent cell   | Target cell | Pathway                  | Potential clinical value                                                                 | Biological function                                                                 | Ref.       |
|--------------------------------------------|------------|---------------|-------------|--------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| Circ-0072088                               | up         | Huh-7         | Hep3B       | miR-375/MMP-16           | Diagnosis and prognosis                                                                   | inhibit the metastasis of HCC cells                                                  | Lin et al. (40) |
| CircUHRF1                                  | up         | HCC cells     | NK cells    | TIM-3/miR-449c-5p       | Therapeutic strategy                                                                      | inhibit NK cell function; drive resistance to anti-PD1 immunotherapy                | Zhang et al. (41) |
| CircANTXR1                                 | up         | Huh-7         | HCCLM3      | miR-532-5p/XRCC5         | Diagnostic biomarker and therapeutic target                                               | facilitate HCC proliferation and metastasis                                          | Huang et al. (42) |
| CircRNA Cdr1as                             | up         | HepG2/SMMC-7721 | 293T cells  | miR-1270/AFP             | Therapeutic target                                                                      | promote the progression of HCC                                                        | Su et al. (43) |
| CircRNA-SORE (circRNA-104797 or circ_0087293) | up         | sorafenib-resistant HCC cells | HCC cells | PRP19/YBX1               | Sorafenib resistance monitoring                                                          | sorafenib resistance in HCC                                                         | Xu et al. (44) |
| circTMEM45A (hsa_circ_00666659)            | up         | MHC97H cells  | Hep3B       | miR-665/IGF2             | Diagnostic biomarker and therapeutic target                                               | promote HCC progression                                                               | Zhang et al. (45) |
| hsa_circ-0004277                           | up         | HepG2 and SMMC-7721 cells | HL-7702 cells | ZO-1/EMT                | Therapeutic target                                                                      | promote the proliferation and migration of HCC cells                                 | Zhu et al. (46) |
| hsa_circ_0061395                           | up         | –             | –           | miR-877-5p/PIK3R3        | New perspective                                                                         | facilitate HCC progression                                                            | Yu et al. (47) |
| CircWHSC1                                  | up         | –             | –           | HOXA1/miR-142-3p         | Diagnostic marker                                                                       | facilitate HCC cell growth and metastasis                                             | Lyu et al. (48) |
| CircWDR25 (hasa_circRNA-0004310)           | up         | Hep3B, SMMC-7721, HCCLM3 | LX-2        | –                       | Prognostic marker                                                                       | Participate in the occurrence and development of HCC                                 | Liu et al. (49) |
| hsa_circ_0070396                           | up         | –             | –           | –                       | Diagnostic biomarker                                                                    | promote the progress of HCC                                                            | Lyu et al. (50) |
| hsa_circ_0074854                           | up         | HepG2         | macrophages | HuR/macrophage M2        | Diagnostic and therapeutic marker                                                         | enhance migration, invasion, and EMT of HCC cells                                    | Wang et al. (51) |
| circFBIM1                                   | up         | –             | SNU-387 and HuH7 cells | miR-338/LRP6             | Therapeutic target                                                                      | promote HCC progression and glycolysis                                               | Lai et al. (51) |
| circRNA-100338                             | up         | Hep3B and MHC97H cells | HUVEC       | proangiogenic activity   | Risk indicator                                                                          | enhance angiogenesis and HCC metastasis                                              | Huang et al. (52) |
| Circ-ZNF652                                 | up         | HCC cells     | SNU-387 and HuH7 cells | miR-29a-3p/GUICD1        | Therapeutic target                                                                      | contribute to HCC cell proliferation, migration, and glycolysis                      | Li et al. (11) |
| hsa_circ_0004658                           | up         | macrophages   | SMMC-7721 and HepG2 | miR-499b-5p/JAM3         | Diagnostic biomarker and therapeutic target                                               | inhibit tumor progression and promote apoptosis in HCC cells                         | Zhang et al. (53) |
| Circ-DB                                    | up         | adipocytes    | HCC cells   | miR-34a/USP7/Cyclin A2   | Risk indicator                                                                          | promote HCC growth and reduces DNA damage                                             | Zhang et al. (6) |
| Circ_MMP2 (hasa_circ_0039411)               | up         | 97H or LM3 cell | L02 and HepG2 | MMP2/miR-136-5p         | Therapeutic target                                                                      | promotes HCC metastasis                                                              | Liu et al. (54) |
| circAKT3                                   | up         | –             | –           | –                       | Prognostic marker                                                                       | associate with a higher risk of HCC recurrence and mortality                         | Luo et al. (55) |
| DECs                                       | up         | –             | –           | targeting miRNAs/VEGF/VEGFR, PI3K/Akt, etc. | Diagnostic biomarker                                                                   | affect the occurrence and progression of HCC                                        | Sun et al. (56) |
| hsa_circ_00044001                          | up         | LM3 cell      | HepG2, and 97 L cells | miR449a-MET             | Prognostic marker                                                                        | enhance the potential of cell migration and invasion                                  | Wang et al. (57) |
| hsa_circ_0057929                           | up         | normal cells  | HCC cells (Huh7 and Hep3) | BAK1/miR-331-3p         | Prognostic biomarker and therapeutic target                                               | suppress HCC progression                                                              | Chen et al. (58) |
| hsa_circ_0028861                           | down       | normal cells  | HCC cells (Huh7 and Hep3) | miR-1254, miR-3141-5p/integrin, VEGF, PI3K/Akt, mTOR, etc. | Diagnostic Biomarker                                                                   | influence HCC progression and downstream tumor-related signaling pathways            | Wang et al. (12) |

- not provided.
Some exosome circRNAs can act on target cells or organs through the transport of exosomes, and then participate in the regulation of proliferation, apoptosis, invasion, metastasis, and glycolysis of HCC cells. Hsa_circ_0004658 secreted by RBPJ overexpressed macrophages can inhibit proliferation and induce apoptosis in HCC cells by sponging miR-499b-5p and downregulating JAM3 expression (53). Circ_0061395 was upregulated in serum exosomes of HCC patients. Circ_0061395 inhibition reduced malignant behavior of HCC cells, induced cell cycle arrest, apoptosis, repressed proliferation, invasion, and migration of HCC cells, by regulating the miR-877-5p/PIK3R3 axis (47). Circ-ZNF652 was upregulated in the exosomes derived from HCC patients and HCC cells. Circ-ZNF652 was a sponge of miR-29a-3p, and GUCD1 was a target gene of miR-29a-3p. Therefore, circ-ZNF652 contributed to HCC cell proliferation, migration, invasion, and glycolysis by regulating the miR-29a-3p/GUCD1 axis (11). Circumstances were also involved in the transport of circANTXR1 in HCC cells. Huang et al. (42) found that MiR-532-5p could be sponged by circANTXR1 and XRCC5 was a target of miR-532-5p. They indicated circANTXR1 silencing can inhibit HCC cell proliferation in vitro and suppress HCC tumor growth in vivo through the miR-532-5p/XRCC5 axis. CircTMEM45A and CircWHSC1 expressions were upregulated in HCC tissues and cells. CircWHSC1 played a tumor-promoting role in HCC by elevating HOXA1 through sponging miR-142-3p, and circTMEM45A acted as a miR65 sponge to relieve the repressive effect of miR-665 on its target insulin growth factor 2 (IGF2), upregulation of IGF2 and HCC progression (45, 48). Additionally, circ0051443 was mainly packaged in exosomes and significantly lower in the plasma and tissues of patients with HCC compared with healthy controls. Circ-0051443 was transmitted from normal cells to HCC cells via exosomes and suppressed the malignant biological behavior by promoting cell apoptosis and arresting the cell cycle (58).

Exosomes produced by tumor cells play a role in epithelial–mesenchymal transition (EMT) and tumor metastasis (60). Widespread metastases remain a major challenge for therapy and prognosis of HCC (2). EMT is an important biological process that is closely associated with cell migration and invasion (11). Increasing evidence indicates that exosomal circRNAs derived from tumor cells participate in EMT and tumor metastasis and provide a new mechanism for the interaction between liver cancer metastasis and angiogenesis (46, 52). Huang et al. (52) first found the overexpression or knockdown of exosomal circRNA-100338 significantly enhanced or reduced the proliferation, angiogenesis, permeability, and metastasis of HCC cells. Additionally, they also observed that sustained high expression of exosomal circRNA-100338 in the serum of HCC patients undergoing radical hepatectomy may be a risk indicator of lung metastasis and poor survival rate. In the study by Zhu et al. (46), circ-0004277 was significantly upregulated in HCC cells, tissues, and plasma exosomes, while circ-0004277 overexpression significantly induced EMT-related transcription factor ZEB-1 upregulated and ZO1 downregulated. Then they suggested the overexpression of
circ-0004277 enhanced the proliferation, migration, and EMT of HCC cells in vivo and in vitro by inhibiting ZO-1 and promoting EMT progression (46). The findings by Liu et al. (54) suggest that cell migration, invasion, and EMT progress were promoted after circ_MMP2 was delivered by 97H- or LM3-secreted exosomes into L02 and HepG2 cells by sponging miR-136-5p to enhance MMP2 expression.

Since HCC is a highly heterogeneous cancer, patients with HCC show varying sensitivity to treatment options (60). Additionally, the high recurrence rate of HCC leads to poor prognosis. There is an urgent need for new prognostic biomarkers to help identify drug resistance and recurrence. Zhang et al. (41) reported that exosomal circUHRF1 was predominantly secreted by HCC cells, circUHRF1 inhibited NK cell function by upregulating the expression of TIM-3 via degradation of miR-449c-5p, thereby promoting immune evasion and resistance to anti-PD1 immunotherapy in HCC. Sorafenib has shown survival benefits for individuals with advanced HCC, suggesting that molecular-targeted therapies could be effective in this chemoresistant cancer (61). However, sorafenib resistance significantly limits its therapeutics efficacy. Xu et al. (44) found that circRNA-SORE was upregulated in sorafenib-resistant HCC cells and transported by exosomes to spread sorafenib resistance among HCC cells. CircRNA-SORE bonded with the oncogenic protein YBX1 and blocked PRP19-mediated YBX1 degradation. They suggested that sorafenib resistance could be overcome by targeting circRNA-SORE or YBX1. Luo et al. (55) found the expression of exosomal circAKT3 in HCC patients was significantly increased compared with healthy subjects, and HCC patients with high exosomal circAKT3 had higher tumor recurrence rates and higher mortality.

**RELATIONSHIPS BETWEEN EXOSOMAL CIRC RNAS AND CLINICOPATHOLOGICAL CHARACTERISTICS IN HCC**

In Table 2, we summarized the relationships between exosomal circRNA expression and clinicopathological characteristics of HCC patients. Zhang et al. (41) explored the relationship between circUHRF1 expression and the clinicopathological characteristics of 240 HCC patients, and their results showed that HCC patients with circUHRF1 high expression had a larger tumor size and more microvascular invasion than those with circUHRF1 low expression. The study by Lyu et al. (50) showed that a higher expression level of exosomal circ_0070396 was closely related to tumor size and liver encapsulation invasion. However, the exosomal circRNA-SORE and has_circ_0028861 had no correlation with tumor size, tumor node metastasis (TNM), lymph node metastasis (LNM), vascular invasion, and extrahepatic metastasis (12, 44). Huang et al. (52) found that the high expression rate of circRNA-100338 in the serum of HCC patients at three weeks post-operation was closely associated with TNM stages, vascular invasion, extrahepatic metastasis, and satellite foci, but not with gender and age. In another study, the expressions of exosomal circ-0072088, circUHRF1, circTMEM45A, hsa_circ_0061395, and hsa_circ_0004001 were significantly upregulated in patients with HCC and positively correlated with TNM stages and tumor size but not with gender or age. In addition, the expression of circTMEM45A was also related to vascular invasion (40, 42, 45, 47, 56). Furthermore, high levels of hasa_circ_0004123 and hsa_circ_0075792 expression were positively correlated with tumor size and the TNM stages, but not with age, gender, and LNM (56). These existing bodies of evidence stated that TNM stage, tumor size, and vascular invasion were most closely related to the abnormal expressions of exosomal circRNAs, but age, gender, number of tumors, and LNM showed no significant relationship.

### THE DIAGNOSTIC AND PROGNOSTIC VALUES OF EXOSOMAL CIRC RNAS IN HCC

Despite advances in medical, locoregional, and surgical therapies, HCC remains to be high mortality due to the recurrence and metastasis after surgical resection (61). HCC derived exosomes could redirect metastasis of tumor cells which lack the ability to

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**TABLE 2 | Relationship between exosomal circRNAs and clinicopathological characteristics in HCC.**

| circRNAs          | Expression | N(L/H) | Gender | Age | TS | TNM | LNM | NT | LC | VI | EM | SF | Ref. |
|-------------------|------------|--------|--------|-----|----|-----|-----|-----|----|----|----|----|----|-----|
| circ-0072088      | up         | 25/25  | N      | Y   | Y  | N   | N   | Y  | N  |   |    |    |    |     |
| circUHRF1         | up         | 120/120| N      | Y   | N  | N   | N   | Y  | N  |   |    |    |    |     |
| circANTXR1        | up         | 35/35  | N      | Y   | N  | N   | N   | N  | N  |   | Y  |    |    |     |
| circRNA-SORE      | up         | 30/30  | N      | N   | N  | N   | N   | N  | N  |   |    |    |    |     |
| circTMEM45A       | up         | 34/34  | N      | N   | Y  | Y   | N   | N  | N  |   |    |    |    |     |
| hsa_circ_0061395  | up         | 12/18  | N      | N   | Y  | Y   | N   | N  | N  |   |    |    |    |     |
| hsa_circ_0070396  | up         | 42/69  | N      | N   | Y  | N   | N   | N  | N  |   |    |    |    |     |
| circRNA-100338    | up         | 23/16  | N      | N   | Y  | Y   | N   | N  | Y  | Y |    |    |    |     |
| hsa_circ_0028861  | down       | 56     | N      | N   | N  | N   | N   | N  | N  |   |    |    |    |     |
| hsa_circ_0004001  | up         | 35/36  | N      | Y   | N  | Y   | N   | N  | N  |   |    |    |    |     |
| hsa_circ_0004123  | up         | 36/35  | N      | N   | Y  | N   | N   | N  | N  |   |    |    |    |     |
| hsa_circ_0075792  | up         | 40/31  | N      | N   | N  | Y   | N   | N  | N  |   |    |    |    |     |

Y, correlation; N, no correlation; Number of patients; L/H: low expression/high expression; TS, Tumor size; TNM, Tumor Node Metastasis; LNM, Lymph node metastasis; NT, Number of tumors; LC, Liver cirrhosis; VI, vascular invasion; EM, Extrahepatic metastasis; SF, Satellite foci; -, not provided.
metastasize to a specific organ (62). Exosomes can shuttle circRNAs between cells, and regulate cell differentiation and tissue development (63). Recently, some studies indicated the exosomal circRNAs could serve as biomarkers for the diagnosis and prognosis of HCC (12, 41, 46, 49, 50). We summarized recent studies on exosomal circRNAs as diagnostic and prognostic biomarkers of HCC (shown in Tables 3, 4).

Hsa_circ_0028861 was downregulated in patients with HCC and might influence HCC progression by regulating its targeted miRNAs and downstream tumor-related signaling pathways (12). Wang et al. (12) showed that hsa_circ_0028861 was identified as a novel diagnostic biomarker for HCC diagnosis with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.79 (95 CI%: 0.72–0.87) for discriminating HCC from chronic HBV and cirrhosis individuals, a sensitivity of 67.86% and a specificity of 82.69%. Moreover, Hsa_circ_0028861 could identify small (AUC = 0.81), early-stage (AUC = 0.82), and AFP-negative (AUC = 0.78) HCC. The combination of hsa_circ_0028861 and AFP exhibited better diagnostic ability (AUC = 0.86, a sensitivity of 76.36% and a specificity of 86.27%). Lyu et al. (50) demonstrated that circ_0070396 was upregulated in plasma-derived exosomes and the combination of hsa_circ_0070396 and AFP displayed higher diagnostic value. The combination has higher diagnostic ability with an ROC of 0.9384 (0.9037–0.9732), 0.8499 (0.7893–0.9105), and 0.7476 (0.6719–0.8233), respectively, for distinguishing HCC from healthy donors, chronic hepatitis B, and cirrhosis groups, than single indicators. Circ_0070396 might be a potential diagnostic biomarker for HCC. Additionally, Sun et al. (56) found that hsa_circ_0004001, hsa_circ_0004123, and hsa_circ_0075792 were upregulated in human blood exosomes from patients with HCC. Sun et al. (56) demonstrated that the diagnostic performance of hsa_circ_0004001, hsa_circ_0004123, and hsa_circ_0075792 exhibited higher sensitivity and specificity. When combined with these three biomarkers, the diagnostic performance was further improved to a sensitivity of 90.5% and an AUC of 0.89. They indicated that the combination of the three circRNAs can be used as a valuable diagnostic biomarker in HCC (56). Moreover, Lin et al. (40) showed that circ_0072088 was mainly secreted by HCC cells via exosomes and its expression was significantly higher in HCC tissues and cells than in paracancerous tissue and healthy hepatic cells, and ROC curve analysis showed that circ_0072088 had a high diagnostic value for HCC, with an AUC of 0.899. Some studies discovered that exosome circTMEM45A, circANTXR1, circ-0004277, and circWHSC1 were all upregulated in HCC tissues and cell lines. ROC curves were used to examine their diagnostic values, and they found the AUCs to be 0.888, 0.76, 0.816, and 0.8692, respectively. These results suggest that exosomal circRNAs are diagnostic biomarkers for HCC (42, 45, 46, 48). Furthermore, Chen et al. (58) analyzed the circ-0051443 expression in 60 patients with HCC and 60 healthy subjects, and found that its expression in patients with HCC was significantly lower than that in healthy controls. Circ-0051443 also showed a reliable performance in diagnosing HCC with an AUC of 0.8089.

Liu et al. (49) indicated that high expression of circWDR25 in adjacent tissues was closely related to the poor prognosis of HCC patients after radical hepatectomy. According to Cox regression analyses, circWDR25 was an independent factor for overall survival rate (HR = 1.918; 95% CI: 1.252–2.940, P = 0.003) and tumor free survival (TFS) rate (HR = 1.732; 95% CI: 1.238–2.423, P =0.01) for HCC patients. CircWDR25 has the potential to be used as a screening and monitoring indicator for patients with high recurrence risk HCC. Furthermore, the expression of exosomal circAKT3 in HCC patients was significantly increased compared with healthy subjects. Patients with high

### TABLE 3 | Exosomal circRNAs serve as potential diagnostic biomarkers for HCC.

| CircRNAs | ROC | 95 CI% | Sensitivity (%) | Specificity (%) | Ref. |
|-----------|-----|--------|----------------|-----------------|-----|
| circ-0072088 | 0.899 | – | – | – | Lin et al. (43) |
| circANTXR1 | 0.76 | 0.688–0.8517 | – | – | Huang et al. (42) |
| circTMEM45A (hsa_circ_0066659) | 0.888 | 0.823–0.954 | – | – | Zhang et al. (45) |
| hsa_circ-004277 | 0.816 | 0.741–0.891 | 58.3 | 96.7 | Zhu et al. (46) |
| CircWHSC1 | 0.8692 | – | – | – | Lyu et al. (48) |
| hsa_circ_007096 | 0.8574 | 0.8025–0.9122 | 62.16 | 98.15 | Lyu et al. (50) |
| hsa_circ_007096 + AFP* | 0.9384 | 0.9037–0.9732 | 81.98 | 100 | Lyu et al. (50) |
| hsa_circ_007096 + AFP† | 0.7741 | 0.6955–0.8526 | 76.58 | 68 | Lyu et al. (50) |
| hsa_circ_007096 + AFP‡ | 0.8499 | 0.7893–0.9105 | 71.17 | 86 | Lyu et al. (50) |
| hsa_circ_007096 + AFP§ | 0.6609 | 0.5746–0.7472 | 48.85 | 81.03 | Lyu et al. (50) |
| hsa_circ_007096 + AFP¶ | 0.7476 | 0.6719–0.8233 | 68.47 | 74.14 | Lyu et al. (50) |
| hsa_circ_0051443 | 0.8089 | – | – | – | Chen et al. (59) |
| hsa_circ_0028861 | 0.79 | 0.72–0.87 | 67.86 | 82.69 | Wang et al. (12) |
| hsa_circ_0028861 in AFP (-) HCC | 0.78 | 0.67–0.97 | 71.43 | 80.77 | Wang et al. (12) |
| hsa_circ_0028861 in small HCC | 0.81 | 0.73–0.89 | 70 | 80.77 | Wang et al. (12) |
| hsa_circ_0028861 in Stage (II–III) HCC | 0.82 | 0.74–0.91 | 71.43 | 82.69 | Wang et al. (12) |
| hsa_circ_0028861 + AFP | 0.86 | 0.80–0.93 | 76.36 | 86.27 | Wang et al. (12) |
| hsa_circ_0004001 | 0.79 | – | 76.19 | 81.25 | Sun et al. (56) |
| hsa_circ_0004123 | 0.73 | – | 66.67 | 84.38 | Sun et al. (56) |
| hsa_circ_0075792 | 0.76 | – | 80.95 | 68.75 | Sun et al. (56) |
| hsa_circ_0004001 + hsa_circ_0004123 + hsa_circ_0075792 | 0.89 | – | 90.5 | 76.1 | Sun et al. (56) |

* not provided; The AUCs for distinguishing HCC from HD (*), CHB (†), cirrhosis (‡) groups.
TABLE 4 | Exosomal circRNAs serve as potential prognostic biomarkers for HCC.

| CircRNAs                     | Prognosis | HR    | 95 CI%   | Ref.              |
|------------------------------|-----------|-------|----------|------------------|
| circ-0072088 (low vs. High)  | OS        | 0.475 | 0.245-0.922 | Lin et al. (40)   |
| circUHRF1 (High vs. Low)     | OS        | 1.339 | 0.944-2.045 | Zhang et al. (41) |
| circUHRF1 (High vs. Low)     | PR        | 1.782 | 1.172-2.428 | Zhang et al. (41) |
| circRNA-SORE (High vs. Low)  | RFS       | 2.281 | 1.074-4.845 | Xu et al. (44)    |
| circWDR25 (High vs. Low)     | OS        | 1.918 | 1.252-2.940 | Liu et al. (49)   |
| circWDR25 (High vs. Low)     | DFS       | 1.752 | 1.238-2.423 | Liu et al. (49)   |
| circAKT3 (High vs. Low)      | OS        | 1.89  | 1.04-3.01  | Luo et al. (50)   |
| circAKT3 (High vs. Low)      | RFS       | 3.14  | 1.29-6.21  | Luo et al. (55)   |

OS, Overall Survival; PR, postoperative recurrence; RFS, Progression-Free Survival; DFS, Disease Free Survival.

exosomal circAKT3 had higher risk of tumor recurrence (HR = 3.14; 95% CI: 1.29–6.21, P = 0.012) and mortality (HR = 1.89; 95% CI: 1.04–3.01, P = 0.048) (55). Additionally, the study by Xu et al. (44) on 60 patients with HCC showed that high circRNA-SORE expression was closely associated with sorafenib resistance. In multivariate Cox regression analysis, the expression level of circRNA-SORE was positively correlated with HCC recurrence-free survival (RFS) (HR = 2.28; 95% CI: 1.07–4.845, P = 0.032) for HCC patients. The study by Zhang et al. (41) found increased levels of exosomal circUHRF1, indicated NK cell dysfunction, resistance to anti-PD1 immunotherapy, and high cumulative recurrence (HR = 1.762; 95% CI: 1.172–2.428, P = 0.019) for HCC patients. Besides, Lin et al. (40) found a notably decreased 5-year survival rate in those with high circ-0072088. The results indicated that high expression of circ-0072088 was closely correlated with an unfavorable prognosis and may be involved in the development of HCC. To reduce the risk of recurrence and improve prognosis, a follow-up of HCC patients with high expression of exosomal circRNAs after surgery is needed.

CONCLUSIONS AND OUTLOOKS

HCC exacts a heavy disease burden and is currently the second most common cause of cancer-related deaths worldwide. Most HCC patients are diagnosed at an advanced stage. The risk factors for HCC mainly include chronic hepatitis B, hepatitis C, alcohol addiction, metabolic liver disease, aflatoxins, and aristolochic acid exposure. The therapeutic effect of HCC is poor because of the heterogeneity of the etiology, mutation spectrum, and chemotherapy-resistant nature. Even with complete HCC tumor resection, the carcinogenic tissue microenvironment in the remnant liver can lead to the recurrence of HCC, which progresses to a poor prognosis. Thus, it is necessary to provide specific and early diagnostic biomarkers to detect HCC for more optimal therapies and improved patient prognosis.

CircRNAs are single-stranded RNAs that form covalently closed loops and are stable in exosomes. Exosomes are known as important messengers of the cross-talk between tumor and immune cells. Accumulating studies have demonstrated the promoter or suppressor roles of circRNAs in carcinogenesis, progression, and metastasis of HCC. Exosomal circRNAs have been expressed in HCC tissues, blood, urine, and cell supernatant. The expression dysregulation of exosomal circRNA was tightly related to HCC initiation and progression via various mechanisms. Thus exosomal circRNAs can influence HCC cell proliferation, angiogenesis, metastasis, and other biological processes. This review primarily provides that exosomal circRNAs can serve as diagnostic and prognostic biomarkers for HCC and may be potential therapeutic targets for HCC treatment.

The current research results show that whether as diagnostic and prognostic markers or therapeutic monitoring markers of HCC, exosome derived circRNAs have a good prospect, but they also have many limitations. First, clinical doctors can detect exosomal circRNAs to diagnose early-stage HCC and monitor the recurrence and metastasis of HCC, but the above study results come from some small sample case-control studies or animal or cell experiments, so the findings may be over interpreted. More multicenter and multi-ethnic large cohorts in the future are needed to validate the actual diagnostic or prognostic effects of exosomal circRNAs. Second, there are still abundant exosomes that have not been discovered whose biological function is unknown. Capturing tissue-specific and disease-specific exosomes and measuring exosomal circRNA profiles may be an important strategy to track the incidence, recurrence, and metastasis of HCC. Further understanding of the molecular mechanisms and downstream signaling pathways of these functional circRNAs that have been found will identify the molecular targets for treatment of HCC. Exosomal circRNAs-based therapies may be introduced for the precise treatment of HCC in the future.

AUTHOR CONTRIBUTIONS

ZY and YJ wrote the manuscript. ZY made the figure and tables. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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