Original Article

The effect of the *TP53* and *RB1* mutations on the survival of hepatocellular carcinoma patients with different racial backgrounds

Xiaohui Duan[1#^], Yi Cai[1#], Tingting He[2^], Xiaoliang Shi[2], Juan Zhao[2], Hui Zhang[1], Yao Shen[1], Hongjian Zhang[1], Heng Zhang[1], Wenbin Duan[1], Bo Jiang[1], Xianhai Mao[1^]

[1]Department of Hepatobiliary Surgery/Research Laboratory of Hepatobiliary Tumor, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China; [2]OrigiMed, Shanghai, China

Contributions: (I) Conception and design: X Duan, Y Cai, H Zhang, X Mao; (II) Administrative support: Y Shen, H Zhang, B Jiang; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: H Zhang, W Duan, T He; (V) Data analysis and interpretation: X Shi, J Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contribute equally to this work.

Correspondence to: Xianhai Mao. Department of Hepatobiliary Surgery/Research Laboratory of Hepatobiliary Tumor, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Road, Changsha 410005, China. Email: maoxianhai@yeah.net.

Background: Racial disparities in the survival of patients with hepatocellular carcinoma (HCC) exist. Gene mutations have a profound effect on carcinogenesis, are easily affected by environment and etiology factors, and may result in survival divergences among patients with different racial backgrounds. This report explores the effects of gene mutations on the survival of American Caucasians and Asian patients.

Methods: The sequencing and clinical data of 336 HCC patients were obtained from The Cancer Genome Atlas (TCGA) database. The sequencing data was subject to gene mutation profiling, and an analysis of immune cell infiltration was conducted. A multivariate analysis was performed to assess the independent effects of gene mutations on patients' overall survival (OS) and disease-free survival (DFS).

Results: Asian HCC patients had a significantly higher level of *TP53* mutation frequency than Caucasian HCC patients (Asian *vs.* Caucasian, 39% *vs.* 23%; P=0.003). The *TP53* mutation was associated with shorter OS [hazard ratio (HR), 2.33; 95% confidence interval (CI), 1.36–3.97; P=0.002] and DFS (HR, 2.2; 95% CI, 1.38–3.51; P<0.001) in Caucasian HCC patients, but had no effect on Asian HCC patients' survival. Compared to Asian HCC patients, Caucasian HCC patients with the *TP53* mutation had a decreased proportion of infiltrating M2 macrophages and activating natural killer (NK) cells, and an increased proportion of follicular helper T cells. The *RB1* mutation was associated with shorter OS (HR, 3.37; 95% CI, 1.73–6.57; P<0.001) in Asian HCC patients, and shorter DFS (HR, 2.11; 95% CI, 1.15–3.88; P=0.017) in Caucasian HCC patients. Asian HCC patients with the *RB1* mutation had a decreased proportion of infiltrating CD8 T cells.

Conclusions: The effects of the *TP53* and *RB1* mutations on survival differ among Asian and Caucasian HCC patients.

Keywords: *TP53*; *RB1*; survival; race; immune cells

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^ ORCID: Xiaohui Duan, 0000-0003-4364-4001; Tingting He, 0000-0001-5979-267X; Xiaohai Mao, 0000-0003-4364-4001.

Introduction

With 0.78 million tumor-related deaths each year worldwide, liver cancer is the fourth leading cancer-related death (1). Hepatocellular carcinoma (HCC) accounts for 75–85% cases of liver cancer (1,2). Moreover, the incidence had ethnic difference as which in Asia is higher than that in Europe and America, both in men and women (1). The main risk factors for HCC include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin, obesity/diabetes, and heavy alcohol intake (3). The prognosis for patients with HCC is poor, and HCC patients have a median survival time of approximately 11 months (4). Racial disparities in the survival of patients with HCC exist, and survival is significantly worse in African-American patients and superior in Asian patients, compared with white HCC patients (5-7). Disparities in disease progression raise further difficulties in the monitoring and treatment of HCC.

TP53 is one of the most commonly mutated genes in human cancer (8,9). A study of 12 cancer types with 3,281 tumor samples reported that the average mutation frequency of *TP53* was about 42% (10). The wild-type (WT) *TP53* plays an important role in cell cycle regulation and apoptosis after deoxyribonucleic acid (DNA) damage (11). Cells with DNA damage could escape from apoptosis in the absence of functional TP53 and transform into cancer cells (12). Mutations of *TP53* are generally associated with poor prognosis. Indeed, several studies have reported that *TP53* mutations are associated with poor survival in HCC patients (13-16). Additionally, evidence also suggests that the *TP53* mutation is correlated with tumor stage, tumor differentiation, and vascular invasion in HCC (17,18).

RB1 is another frequently mutated tumor suppressor gene in HCC. RB1 functions as a negative regulator of cell cycle progression through the control of the E2 factor (E2F) family of transcription factors (19,20). Many transcription target genes of RB1/E2F are involved in DNA replication, DNA damage response, and cell cycle progression (21,22). Functional RB1 is important for the expression of these genes, and the disorder of RB1 is associated with cancer genesis and an aggressive cancer phenotype (23,24). In HCC, patients with an *RB1* mutation have a poor prognosis (25).

The disruption of specific genes has profound effects on the responses of cells to genotoxic damage. The interaction of gene mutations with environmental and etiologic factors is important for carcinogenesis, and varies among geographic regions, and racial and ethnic groups (16). This study sought to explore the effects of gene mutations among patients with different racial backgrounds. Furthermore, we explored the relationship between mutations and survival among racial backgrounds. The sequencing and clinical data of 336 HCC patients were obtained from The Cancer Genome Atlas (TCGA) database and subject to a survival analysis. Ribonucleic acid (RNA)-sequencing data were extracted and used to analyze the infiltration of immune cells.

We present the article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-312).

Methods

Clinical cohorts

To analyze the relationship between gene mutations and HCC patients' survival, the sequencing and clinical data of 336 HCC patients were obtained from TCGA website (https://portal.gdc.cancer.gov/repository) (up to March 20th, 2020) (26). Data on the overall survival (OS) of all patients and the disease-free survival (DFS) of 294 HCC patients were available. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Estimation of immune cell infiltration

Three hundred and twenty-four HCC samples had RNA-sequencing data available. CIBERSORT was used to assess the proportions of 22 infiltrating immune cell types, which contained myeloid subsets, plasma cells, natural killer (NK) cells, B cells, and 7 T cell types (27). This method used a leukocyte gene signature matrix comprising 547 genes to distinguish among different immune cell types. The results showed the proportion of each immune cell type, and the sum of all immune cell types was equal to 1.

Statistics analysis

R software was used to perform the statistical analysis. Kaplan-Meier curves were used to estimate OS and DFS. The log-rank test was used for the statistical analysis, and hazard ratios (HRs) were calculated using the Cox proportional hazards model. Wilcoxon rank-sum tests were performed to analyze the correlation between gene mutations and the proportion of infiltrating immune cells. Fisher's exact tests were performed to analyze differences

Table 1 Baseline patient characteristics

Characteristics	Asian (n=157)	Caucasian (n=179)
Age	55.0±11.6	63.8±13.2
Gender		
Male	123	101
Female	34	78
HBV		
Positive	89	11
Negative	56	162
NA	12	6
HCV		
Positive	8	34
Negative	137	139
NA	12	6
Alcohol consumption		
Yes	43	65
No	102	108
NA	12	6
Stage		
I	80	76
II	34	41
III/IV	41	44
NA	2	18

HBV, hepatitis B virus; HCV, hepatitis C virus.

in gene mutation frequency among patients with different racial backgrounds. For the analysis, a P value below 0.05 was considered significant.

Results

Cohort characteristics

We used the public data set from TCGA of 336 HCC patients. The characteristics of TCGA HCC population are set out in *Table 1*. Patients were divided into two groups (i.e., Asian or Caucasian) according to race. Patients' had mean ages (± standard deviation) of 55.0±11.6 and 63.8±13.2 in the Asian and Caucasian groups, respectively. The most prevalent history HCC risk factor was HBV in the Asian group (60.0%), and alcohol consumption in the Caucasian group (37.6%).

Gene mutation and survival

In this analysis, gene mutation contained missense, truncation, in-frame shift, fusion, and copy number variation. The most frequently mutated genes in the Asian group were *TP53* (39%), *CTNNB1* (26%), *PCLO* (12%), *RB1* (12%), and *ALB* (11%) (see *Figure 1*). Conversely, the most frequently mutated genes in the Caucasian group were *CTNNB1* (26%), *TP53* (23%), *ALB* (15%), *LRP1B* (12%), and *PREX2* (12%) (see *Figure 1*). *TP53* was the only frequently mutated gene for which the mutation rate was significantly higher in Asian patients than Caucasian patients (39% *vs.* 23%; P=0.003). Caucasian patients with the *TP53* mutation had significantly shorter OS [HR, 2.33;

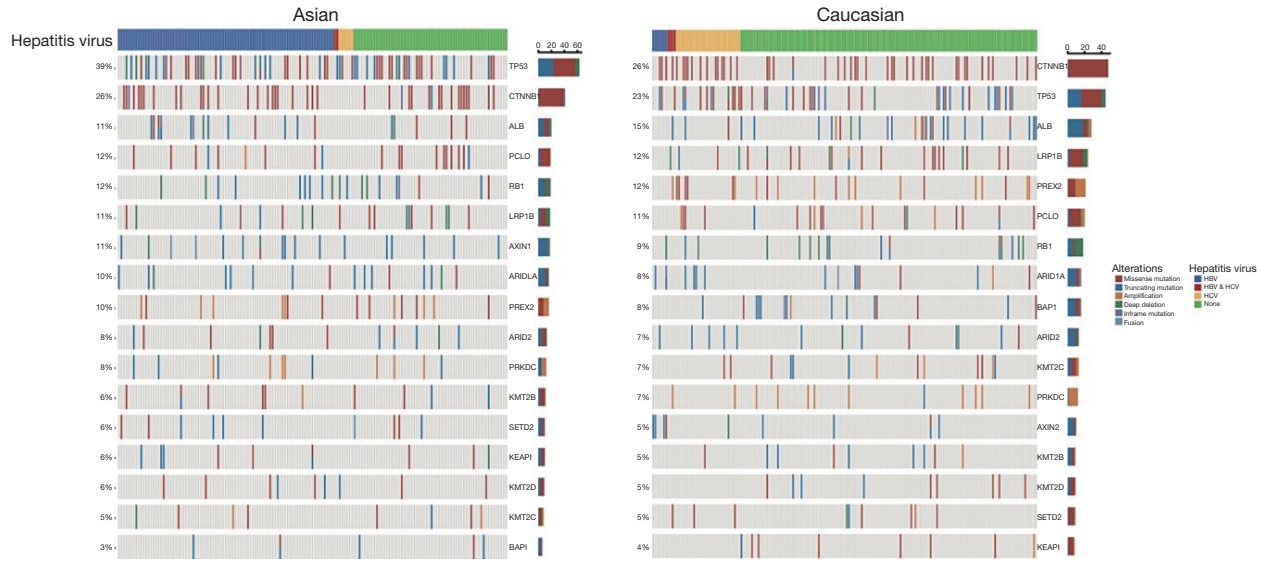

Figure 1 Gene mutation frequency in patients with HCC. HCC, hepatocellular carcinoma.

95% confidence interval (CI), 1.36–3.97; P=0.002; see *Figure 2A*] than Asian patients with the *TP53* mutation. However, there was no significant difference between WT *TP53* and mutated *TP53* in Asian patients (HR, 1.72; 95% CI, 0.95–3.14; P=0.075; see *Figure 2B*). In relation to the *RB1* mutation, the results were reversed; that is, Asian patients with the *RB1* mutation had an obviously shorter OS (HR, 3.37; 95% CI, 1.73–6.57; P<0.001; see *Figure 2C*) than Caucasian patients with the *RB1* mutation. Indeed, the *RB1* mutation had no effect on Caucasian patients' OS (HR, 1.04; 95% CI, 0.45–2.4; P=0.924; see *Figure 2D*). To assess the independence of *TP53* and *RB1*, we used a multivariable Cox proportional hazards model, adjusting for age, gender, HBV, HCV, alcohol consumption, and stage. After adjustments, the *RB1* mutation was still found to be correlated with shorter OS (HR, 2.67; 95% CI, 1.23–5.8; P=0.013; see *Figure 3*) in Asian patients, and the *TP53* mutation was found to be correlated with a shorter OS (HR, 2.11; 95% CI, 1.13–3.97; P=0.02; see *Figure 4*) in Caucasian patients. Thus, the *RB1* and *TP53* mutations appear to be independently associated with shorter OS in Asian and Caucasian patients, respectively.

DFS data was available for a majority of the patients (140/157 Asian patients and 154/179 Caucasian patients). Thus, we also analyzed the relationship between gene mutations and patients' DFS. The results of the statistical analysis for DFS differed to those for OS. Neither the *TP53* (HR, 1.56; 95% CI, 0.98–2.5; P=0.061; see *Figure 5A*) nor the *RB1* (HR, 1.71; 95% CI, 0.87–3.35; P=0.121; see *Figure 5B*) mutations correlated with significantly different DFS compared with WT in Asian patients. In Caucasian patients, both the *TP53* (HR, 2.2; 95% CI, 1.38–3.51; P<0.001; see *Figure 5C*) and the *RB1* (HR, 2.11; 95% CI, 1.15–3.88; P=0.017; see *Figure 5D*) mutations were associated with shorter DFS. We also used a multivariable Cox proportional hazards model to assess the independence of the *TP53* and the *RB1* mutations. After adjustment, the *TP53* (HR, 2.10; 95% CI, 1.24–3.6; P=0.006; *Figure 6*) and *RB1* (HR, 2.14; 95% CI, 1.06–4.3; P=0.034; *Figure 6*) mutations were still correlated with shorter DFS in Caucasian patients.

TP53 and RB1 mutations have different effects on Asian and Caucasian patients' tumor microenvironments

Using the CIBERSORT algorithm, we calculated the proportion of 22 infiltrating immune cell types in Asian and Caucasian HCC patients. Immune cell infiltration is key biomarkers to the prediction of clinical outcome and development of immunotherapies. Variations in the proportions of tumor infiltrating immune cells might reflect an intrinsic feature of different patients, and correlate with patients' responses to treatments. Asian patients with mutated *TP53* had relatively higher proportions of M0 macrophages and neutrophils (see *Figure 7A,B*), while the proportion of naïve B cells was decreased (see *Figure 7C*). The *RB1* mutation in Asian patients was correlated with fewer infiltrating CD8 T

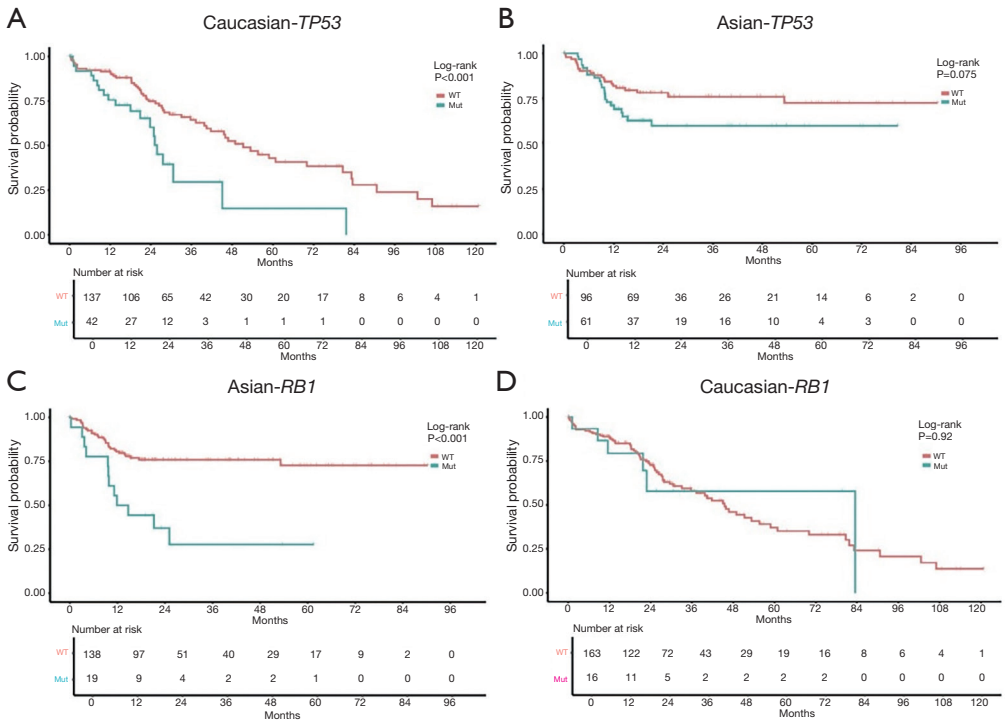

Figure 2 Kaplan-Meier survival curve estimates of OS of *TP53* mutations in Asian patients (A) and Caucasian patients (B), and *RB1* mutations in Asian patients (C) and Caucasian patients (D). OS, overall survival.

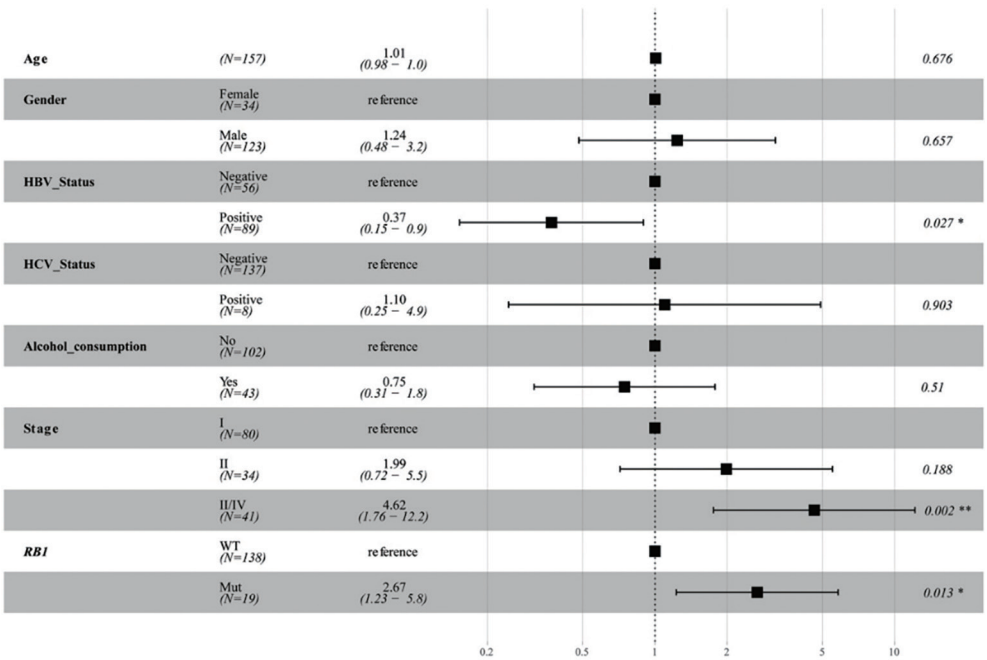

Figure 3 Multivariate analysis of OS in Asian patients with HCC. OS, overall survival; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

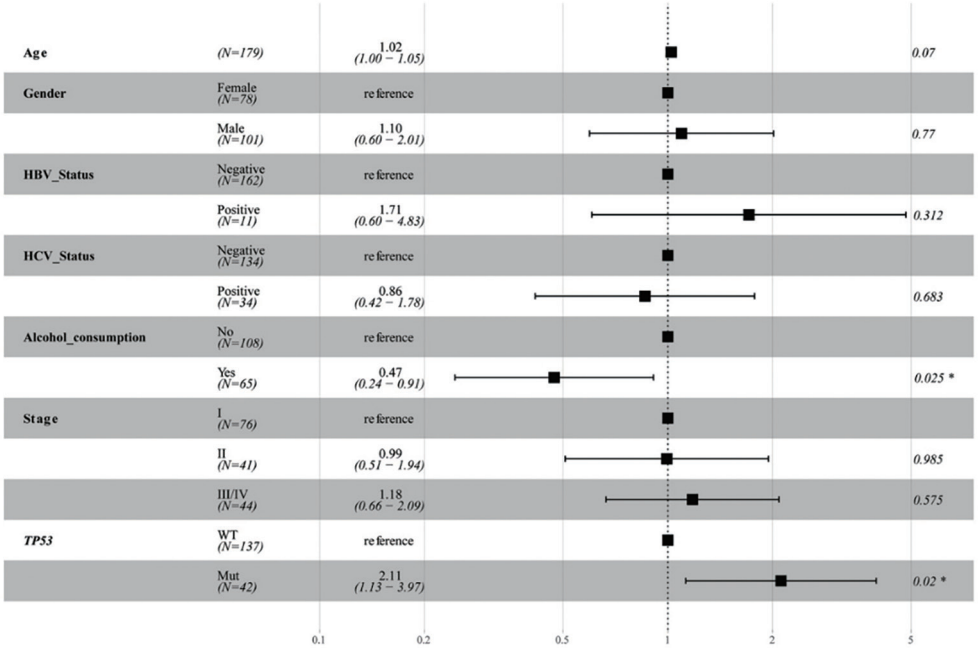

Figure 4 Multivariate analysis of OS in Caucasian patients with HCC. OS, overall survival; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

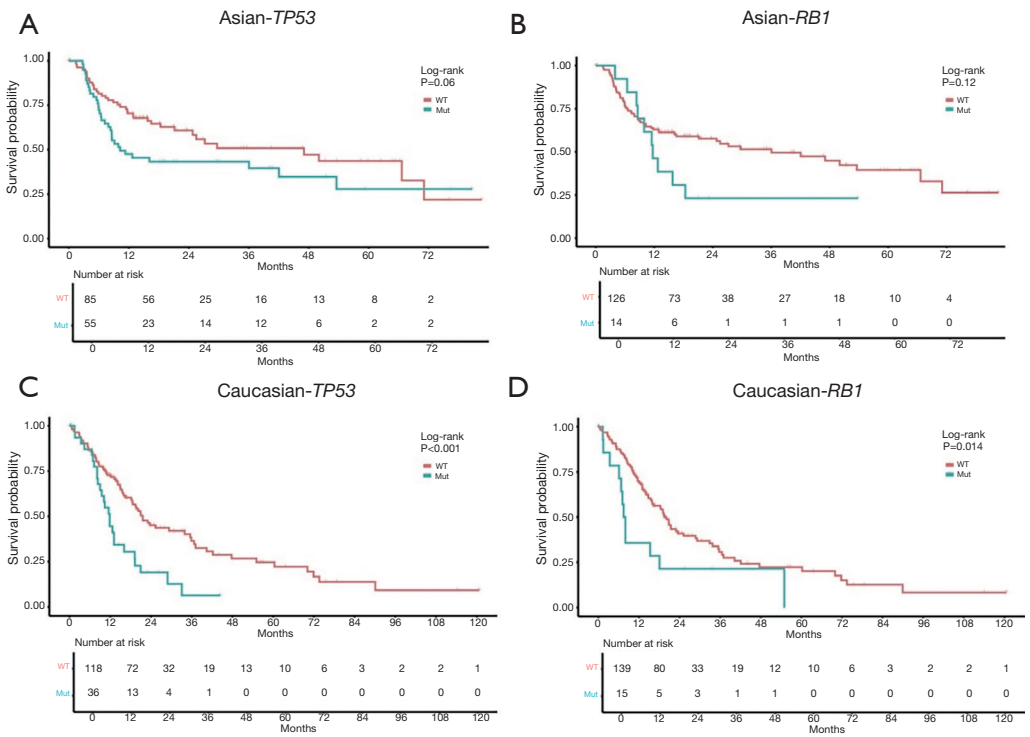

Figure 5 Kaplan-Meier survival curve estimates of DFS of Asian patients with the *TP53* (A) or *RB*1 (B) mutations, and Caucasian patients with the *TP53* (C) or *RB1* (D) mutations. DFS, disease-free survival.

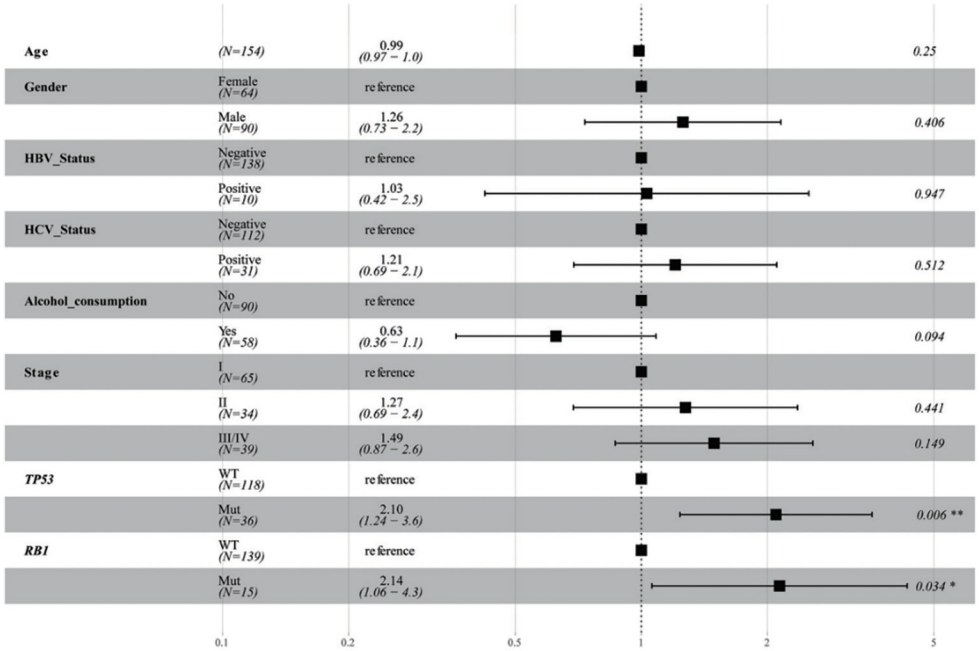

Figure 6 Multivariate analysis of DFS in Caucasian patients with HCC. DFS, disease-free survival; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

cells in Asian patients (see *Figure 7D*). In relation to Caucasian patients, *TP53* was correlated with increased proportions of M0 macrophages and follicular helper T cells (see *Figure 7E,F*). Additionally, the proportions of M2 macrophages and activated NK cells were decreased (see *Figure 7G,H*). However, no difference in immune cell infiltration was found between the *RB1* mutation and WT sub-cohort in the Caucasian HCC patients. Thus, the *TP53* and *RB1* mutations appear to have divergent effects on immune infiltration in patients of different races.

Discussion

There was no major divergence in the frequently mutated genes of Asian and Caucasian HCC patients. Of the 17 most commonly mutated genes, only the mutation rate of *TP53* was significantly higher in Asian HCC patients than Caucasian HCC patients (39% *vs.* 23%; P=0.003). Thus, carcinogenic-driver gene mutations in HCC patients are hardly affected by racial background.

Consistent with previous reports (15,28), Caucasian HCC patients with the *TP53* mutation were found have significantly shorter DFS (HR, 2.2; 95% CI, 1.38–3.51; P<0.001) and OS (HR, 2.33; 95% CI, 1.36–3.97; P=0.002) than those with WT *TP53*. Several studies have indicated that Japanese (16,29,30) and Chinese (31) HCC patients with the *TP53* mutation have a poor prognosis. However, in this study, we found that Asian patients with the *TP53* mutation have a relatively shorter DFS (HR, 1.56; 95% CI, 0.98–2.5; P=0.061) and OS (HR, 1.72; 95% CI, 0.95–3.14; P=0.075) than those with WT *TP53*. However, these results, which are inconsistent with those of previous studies, may be attributable to the heterogeneity of Asian patients' composition in America and the limited sample size (n=175).

To explore the intrinsic difference between these two groups of patients with the *TP53* mutation, we used a CIBERSORT algorithm to calculate the proportions of 22 types of tumor infiltrating immune cells. Asian patients with the *TP53* mutation had significantly higher proportions of M0 macrophages and neutrophils, and a lower proportion of naïve B cells. Tumor-associated neutrophils could recruit macrophages to promote the progression of HCC and are resistant to sorafenib (32). High levels of macrophages (33) and neutrophils (34) are associated with poor prognosis in HCC patients. In addition, a high density of tumor infiltrating naïve B cells was found to be associated with superior survival (35). These findings suggest that the

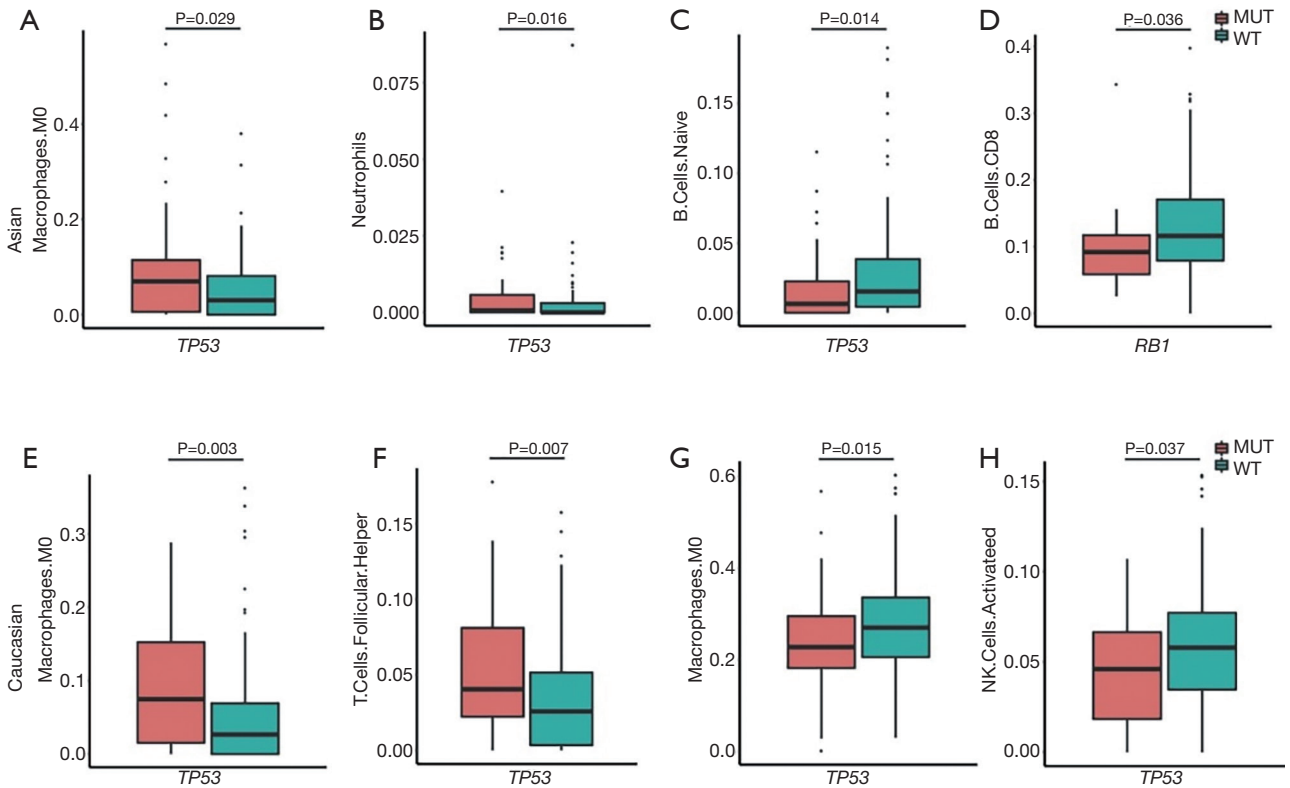

Figure 7 Immune cell infiltration in Asian and Caucasian patients with the *TP53* or *RB1* mutations. Infiltrating M0 macrophages (A), neutrophils (B), naïve B cells (C) in Asian patients with the *TP53* mutation. Infiltrating CD8 T cells (D) in Asian patients with the *RB1* mutation. Infiltrating M0 macrophages (E), follicular helper T cells (F), M2 macrophages (G), activating NK cells (H) in Caucasian patients with the *TP53* mutation. NK, natural killer.

TP53 mutation is associated with a poor prognosis in Asian patients. However, the survival analysis did not support this finding, as the results did not reach statistical significance. The use of proportions of immune cells and the small sample size of the present study limit interpretations of these results. An immunohistochemistry verification of the composition of the immune cells and a lager cohort for the survival analysis is needed. Caucasian patients with the *TP53* mutation have increased proportions of M0 macrophages and follicular helper T cells, and decreased proportions of M2 macrophages and activating NK cells. The impaired function of activating NK cells (36,37) has been found to be associated with HCC progression and worse survival. Collectively, these results suggest that *TP53* might play a role in the regulation of immune cell infiltration and is associated with poor prognosis in Caucasian HCC patients.

Preclinical research has reported that *RB1* loss abrogates cell cycle control and genome integrity, and promotes liver carcinogenesis (23). In addition, clinical research has indicated that *RB1* dysfunction is associated with worse survival in resectable HCC (25). Asian patients with the *RB1* mutation have significantly shorter OS (HR, 3.37; 95% CI, 1.73–6.57; P<0.001) than those with WT *RB1*, but no such effect was observed among Caucasian patients (HR, 1.04; 95% CI, 0.45–2.4; P=0.924). The results in relation to DFS were reversed; that is, Caucasian patients with the *RB1* mutation had significantly shorter DFS (HR, 2.11; 95% CI, 1.15–3.88; P=0.017), but no such effect was observed among Asian patients (HR, 1.71; 95% CI, 0.87–3.35; P=0.121). These results suggest that the *RB1* mutation reduced the quality of lives of Caucasian patients and the survival time of Asian patients. Asian patients with the *RB1* mutation had a significantly decreased proportion of CD8 T cells (P=0.036) than those WT *RB1*. The augmentation of CD8 T cells has been found to be associated with a favorable prognosis in HCC (38-40). A decreased proportion of CD8 T cells is consistent with a poor prognosis among Asian patients with the *RB1* mutation.

It should be noted that this study had a number of limitations. First, the sample sizes of the Asian (n=157) and Caucasian (n=179) subgroups were limited. Second, although the clinical diagnosis and treatment methods of HCC in the East and the West are basically the same according to guideline, patients with different racial backgrounds may have different medical decisions due to economic reasons and different access to medical care, which may affect survival. Finally, proportions of infiltrating immune cells were used for comparisons; however, the sums of infiltrating immune cells varied among different patients; thus, quantitative analyses need to be undertaken.

To conclude, we observed that the *TP53* and *RB1* mutations had discordant effects on the survival of HCC patients with different racial backgrounds, exploring the correlations among gene mutations, races, immune microenvironment and clinical prognosis in HCC patients. In the research and treatment of HCC, more attention needs to be paid to geographic regions, racial, and ethnic groups.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jgo-21-312). TH, XS and JZ report that they are employees of OrigiMed. The other authors report funding from Natural Science Foundation of Hunan Province (Grant Number: 2018JJ3294), Natural Science Foundation of Hunan Province (Grant Number: 2019JJ80007) and Doctor Foundation Project of Hunan Provincial People's Hospital (2020) during the conduct of the study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and informed consent were waived.

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