

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2023 December 27; 15(12): 2674-2961



REVIEW

- 2674 Antimicrobial approach of abdominal post-surgical infections
Fiore M, Corrente A, Di Franco S, Alfieri A, Pace MC, Martora F, Petrou S, Mauriello C, Leone S

MINIREVIEWS

- 2693 Indocyanine green fluorescence in gastrointestinal surgery: Appraisal of current evidence
Kalayarasan R, Chandrasekar M, Sai Krishna P, Shanmugam D
- 2709 Post-cholecystectomy iatrogenic bile duct injuries: Emerging role for endoscopic management
Emara MH, Ahmed MH, Radwan MI, Emara EH, Basheer M, Ali A, Elfert AA

ORIGINAL ARTICLE**Case Control Study**

- 2719 Multidisciplinary diagnosis and treatment nutritional support intervention for gastrointestinal tumor radiotherapy: Impact on nutrition and quality of life
Hui L, Zhang YY, Hu XD

Retrospective Cohort Study

- 2727 Association between the early high level of serum tacrolimus and recurrence of hepatocellular carcinoma in ABO-incompatible liver transplantation
Han JW, Choi JY, Jung ES, Kim JH, Cho HS, Yoo JS, Sung PS, Jang JW, Yoon SK, Choi HJ, You YK
- 2739 Determining the need for a thoracoscopic approach to treat a giant hiatal hernia when abdominal access is poor
Pérez Lara FJ, Zubizarreta Jimenez R, Prieto-Puga Arjona T, Gutierrez Delgado P, Hernández Carmona JM, Hernández Gonzalez JM, Pitarch Martinez M
- 2747 Predictive value of Hajibandeh index in determining peritoneal contamination in acute abdomen: A cohort study and meta-analysis
Hajibandeh S, Hajibandeh S, Evans L, Miller B, Waterman J, Ahmad SJ, Hale J, Higgi A, Johnson B, Pearce D, Helmy AH, Naguib N, Maw A

Retrospective Study

- 2757 Efficacy of pantoprazole plus perforation repair for peptic ulcer and its effect on the stress response
Leng ZY, Wang JH, Gao L, Shi K, Hua HB
- 2765 Application of electroacupuncture in the prevention of low anterior resection syndrome after rectal cancer surgery
Xu LL, Xiang NJ, Cheng TC, Li YX, Chen P, Jiang ZW, Liu XX

- 2774 Effects of remifentanyl combined with propofol on hemodynamics and oxidative stress in patients undergoing resection of rectal carcinoma
Huang J, Tian WJ
- 2783 Percutaneous microwave ablation and transcatheter arterial chemoembolization for serum tumor markers and prognostics of middle-late primary hepatic carcinoma
Lin ZP, Huang DB, Zou XG, Chen Y, Li XQ, Zhang J
- 2792 Novel invagination procedure for pancreaticojejunostomy using double purse string sutures: A technical note
Li J, Niu HY, Meng XK
- 2799 Laparoscopic resection and endoscopic submucosal dissection for treating gastric ectopic pancreas
Zheng HD, Huang QY, Hu YH, Ye K, Xu JH
- 2809 Prediction of the lymphatic, microvascular, and perineural invasion of pancreatic neuroendocrine tumors using preoperative magnetic resonance imaging
Liu YL, Zhu HB, Chen ML, Sun W, Li XT, Sun YS
- 2820 Impact of hepatectomy and postoperative adjuvant transarterial chemoembolization on serum tumor markers and prognosis in intermediate-stage hepatocellular carcinoma
Hu YD, Zhang H, Tan W, Li ZK

Observational Study

- 2831 Analysis of nutritional risk, skeletal muscle depletion, and lipid metabolism phenotype in acute radiation enteritis
Ma CY, Zhao J, Qian KY, Xu Z, Xu XT, Zhou JY

Randomized Controlled Trial

- 2844 Holistic conditions after colon cancer: A randomized controlled trial of systematic holistic care *vs* primary care
Wang J, Qiao JH

Basic Study

- 2855 Mutational separation and clinical outcomes of *TP53* and *CDH1* in gastric cancer
Liu HL, Peng H, Huang CH, Zhou HY, Ge J
- 2866 Hepatic vagotomy blunts liver regeneration after hepatectomy by downregulating the expression of interleukin-22
Zhou H, Xu JL, Huang SX, He Y, He XW, Lu S, Yao B

META-ANALYSIS

- 2879 Recent evidence for subcutaneous drains to prevent surgical site infections after abdominal surgery: A systematic review and meta-analysis
Ishinuki T, Shinkawa H, Kouzu K, Shinji S, Goda E, Ohyanagi T, Kobayashi M, Kobayashi M, Suzuki K, Kitagawa Y, Yamashita C, Mohri Y, Shimizu J, Uchino M, Haji S, Yoshida M, Ohge H, Mayumi T, Mizuguchi T

- 2890 Prognostic role of serum carcinoembryonic antigen in patients receiving liver resection for colorectal cancer liver metastasis: A meta-analysis

Tang F, Huang CW, Tang ZH, Lu SL, Bai T, Huang Q, Li XZ, Zhang B, Wu FX

- 2907 Significance of carcinoembryonic antigen detection in the early diagnosis of colorectal cancer: A systematic review and meta-analysis

Wang R, Wang Q, Li P

CASE REPORT

- 2919 Primary repair of esophageal atresia gross type C *via* thoroscopic magnetic compression anastomosis: A case report

Zhang HK, Li XQ, Song HX, Liu SQ, Wang FH, Wen J, Xiao M, Yang AP, Duan XF, Gao ZZ, Hu KL, Zhang W, Lv Y, Zhou XH, Cao ZJ

- 2926 Portal vein embolization for closure of marked arteriportal shunt of hepatocellular carcinoma to enable radioembolization: A case report

Wang XD, Ge NJ, Yang YF

- 2932 Removal of a large rectal polyp with endoscopic submucosal dissection-trans-anal rectoscopic assisted minimally invasive surgery hybrid technique: A case report

Polese L

- 2938 Successful treatment of invasive liver abscess syndrome caused by *Klebsiella variicola* with intracranial infection and septic shock: A case report

Zhang PJ, Lu ZH, Cao LJ, Chen H, Sun Y

- 2945 Duodenojejunostomy treatment of groove pancreatitis-induced stenosis and obstruction of the horizontal duodenum: A case report

Zhang Y, Cheng HH, Fan WJ

- 2954 Awake robotic liver surgery: A case report

Delvecchio A, Pavone G, Conticchio M, Piacente C, Varvara M, Ferraro V, Stasi M, Casella A, Filippo R, Tedeschi M, Pullano C, Inchingolo R, Delmonte V, Memeo R

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Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Lapo Bencini, PhD, General Surgery Unit, AOUC, Department of Oncology and Robotics, Careggi University Hospital, Florence 350134, Italy. lapbenc@tin.it

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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

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Basic Study

Mutational separation and clinical outcomes of *TP53* and *CDH1* in gastric cancer

He-Li Liu, Huan Peng, Chang-Hao Huang, Hai-Yan Zhou, Jie Ge

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He-Li Liu, Jie Ge, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Huan Peng, Clinical Nursing Teaching and Research Section, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Chang-Hao Huang, Teaching and Research Section of Clinical Nursing, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Hai-Yan Zhou, Department of Pathology, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China

Corresponding author: Jie Ge, MD, Attending Doctor, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, No. 87 Xiangya Road, Kaifu District, Changsha 410008, Hunan Province, China. gejie@csu.edu.cn

Abstract

BACKGROUND

Gastric cancer (GC) is a deadly tumor with the fifth highest occurrence and highest global mortality rates. Owing to its heterogeneity, the underlying mechanism of GC remains unclear, and chemotherapy offers little benefit to individuals.

AIM

To investigate the clinical outcomes of *TP53* and *CDH1* mutations in GC.

METHODS

In this study, 202 gastric adenocarcinoma tumor tissues and their corresponding normal tissues were collected. A total of 490 genes were identified using target capture. Through *t*-test and Wilcoxon rank-sum test, somatic mutations, microsatellite instability, and clinical statistics, including overall survival, were detected, compared, and calculated.

RESULTS

The mutation rates of 32 genes, including *TP53*, *SPEN*, *FAT1*, and *CDH1* exceeded 10%. *TP53* mutations had a slightly lower overall occurrence rate (33%). The *TP53* mutation rate was significantly higher in advanced stages (stage III/IV) than that in early stages (stage I/II) ($P < 0.05$). In contrast, *CDH1* mutations were sig-

nificantly associated with diffuse GC. TP53 is related to poor prognosis of advanced-stage tumors; nevertheless, CDH1 corresponds to a diffuse type of cancer. TP53 is exclusively mutated in CDH1 and is primarily affected by two distinct GC mechanisms.

CONCLUSION

Different somatic mutation patterns in TP53 and CDH1 indicate two major mechanisms of GC.

Key Words: Gastric cancer; TP53 mutation; CDH1 mutation; Clinical outcome; Somatic mutation; Diffuse gastric cancer

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Core Tip: Mutational separation of TP53 and CDH1 in gastric cancer (GC) reveals their distinct mechanisms. TP53 mutations are associated with advanced-stage tumors and poor prognoses, whereas CDH1 mutations are associated with diffuse GC. This study highlights the heterogeneity of GC and provides insights into potential targeted therapies based on specific mutation patterns. Understanding the mutational landscape of TP53 and CDH1 can contribute to personalized treatment approaches for patients with GC.

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INTRODUCTION

Gastric cancer (GC) is one of the most severe malignancies globally, with the fifth leading incidence and highest mortality rates[1]. Global Cancer Statistics in 2018 revealed that GC was the second most prevalent malignant tumor in China, with high morbidity and mortality rates and the third leading cause of cancer-related deaths globally after lung cancer[2,3]. Although it remains unclear, the pathogenesis of GC is caused by several factors, including genetic background and the external environment[4]. Although standardized treatment for GC is continually improving, its overall incidence and mortality rates remain high. The poor prognosis of patients with GC is attributed to limited therapeutic interventions[5, 6]. However, detecting hidden symptoms in the early stages is difficult; hence, most patients are diagnosed at advanced stages[7,8]. The current treatment for GC is primarily surgical resection combined with preoperative or postoperative adjuvant chemotherapy or radiochemotherapy[5,9]. Chemotherapy remains the primary method for postoperative treatment of advanced GC. D2 gastrectomy is the recommended treatment for GC, followed by postoperative adjuvant chemotherapy[10]. However, the tumor response rate to postoperative chemotherapy is low, and patients respond differently to chemotherapy[11,12]. This difference in the response to chemotherapy among patients occurs because GC is a heterogeneous disease that can manifest as differences in gene expression, biological features, and drug sensitivity[13]. Studies on the pathogenesis, biological markers, targeted sequencing, and treatment of GC are advancing given the rapid developments in molecular biology, genomics, bioinformatics, and high-throughput next-generation sequencing. Specifically, advancements in individualized treatment and precision medicine for tumors underscore the need to understand the biological characteristics of GC.

The activation of oncogenes or inactivation of tumor suppressor genes caused by somatic gene mutations modulate the development of malignant tumors, as shown by in depth research on the molecular basis of GC[14]. Therefore, identifying potential driver genes and mutations associated with GC is key to understanding the mechanism of GC occurrence and development, as well as in formulating a follow-up treatment scheme. In this study, target-capture sequencing was used to sequence 490 genes from 202 gastric adenocarcinoma (GAC) cases and adjacent tissue samples to detect somatic mutations.

MATERIALS AND METHODS

Samples

This study enrolled 202 patients with GAC comprising 135 and 67 male and female patients, respectively, who underwent surgery at the Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, China, between January 1, 2014, and December 31, 2015. Primary GAC tumor tissues and matched non-cancerous (NC) tissues located at least 5 cm away from the tumor core were obtained after surgical resection, immediately processed, and stored for subsequent use. None of the recruited patients received chemotherapy or radiotherapy before surgery. Histopathological diagnosis was performed preoperatively and confirmed surgically based on the World Health Organization Classification of Tumors[15]. Tumor stage was defined according to the eighth IASLC (international association for the study of lung

cancer)/AJCC (American joint committee on cancer) staging system[16]. Written informed consent was obtained from each patient prior to surgery. This study was approved by the Research Ethics Committee of Central South University (NO. 2023087), China. All specimens were handled and anonymized according to ethical and legal guidelines.

Experiments

DNA was extracted from the cancer and NC tissues using a customized panel from Roche NimbleGen, Inc. The customized panel included the exons and hotspots of 490 genes, with a total length of 1 Mb. An $\times 10$ sequencer (Illumina Inc.) was used for sequencing in the PE150 mode. All patients underwent curative resection; 27 IA-stage patients did not receive comprehensive treatment, 22 IB-stage patients received S1 chemotherapy, and patients with stage II and above received SOX chemotherapy. After treatment, the patient follow-ups were conducted *via* phone calls and online contact.

Sequencing data analysis

Mapping and somatic mutation calling: quality control was performed on raw sequencing data using FastQC[17]; and the sequences were trimmed for adapters and low-quality bases using Trimmomatic, version 0.38, HEADCROP:3 LEADING:3 TRAILING:3 SLIDINGWINDOW:4:15 MINLEN:36[18]. The trimmed reads were then aligned to GRCh37/hg19 using BWA-MEM version 0.7.17[19]. PICARD[20] was used to add read groups and mark the duplicates. The Genome Analysis Toolkit version 3.8[21] was used for realignment of the indel area and base quality recalibration. The Genome Analysis Toolkit was also used for germline and somatic variant calling with Haplotype Caller and MuTect2, respectively. The variants were annotated using ANNOVAR[22].

Microsatellite instability (MSI) detection: Five commonly used MSI sites, BAT25, BAT26, NR21, NR24, and MONO27, were used for detection. MSI-high (MSI-H) and MSI-low (MSI-L) were selected if at least two loci between the cancer and NC tissues was correspondingly unstable.

Statistical analysis

All statistical analyses were performed using the SPSS software package (version 23.0 (SPSS Inc., Chicago, IL, United States) and R [R Core Team (2018). R: Language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org/>]. Quantitative data are presented as mean \pm SD. Pearson's Chi-squared test was used to compare the difference among ranked data, whereas the one way analysis of variance test was performed to compare the differences among quantitative data. Survival analyses were performed using the Kaplan–Meier method and compared using the Wilcoxon log-rank test. $P < 0.05$ indicated statistically significant differences. For survival analysis, overall survival (OS) was defined as the period from the date of pathological diagnosis to the date of death or last follow-up. The cause of death in this study was the aggravation of GC.

RESULTS

Sample and sequencing statistics

The average age of the cohort was 55.53 ± 10.25 years, range 26–82 years. Tumor diameters were < 5 cm in 158 patients and ≥ 5 cm in 44 patients. There were 39 and 163 cases in the medium-to-high and low differentiation groups, respectively. In terms of TNM stage, 94 and 108 patients were classified with stage I/II and III/IV disease, respectively. Local lymph node metastasis was detected in 127 patients, and no metastasis was observed in 75 patients.

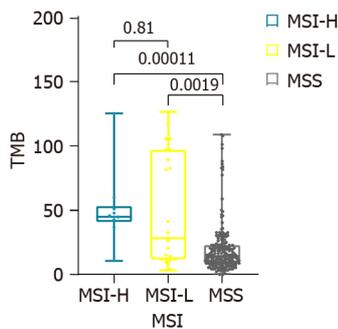
In all tumor and NC samples, the average sequencing base was 2.17 Gb and 1.19 Gb, and the mean sequencing depths were $829 \times$ and $457 \times$ respectively. In the target area, each pair of samples exhibited a mean somatic mutation of 23.1. Among all mutations, point mutations constitute the majority[23], of which missense mutations account for the largest fraction[24]. Small indels primarily comprise of frameshift mutations. Among the point mutations, the order of mutation type sorted by proportion was $C > T$, followed by $T > C$, and $T > G$. Simultaneously, the ratio of $C > T$ mutations is related to age. Older patients had a larger ratio of $C > T$ mutations, possibly because of somatic methylation and lifespan. All sites were stable between tissues and the samples were microsatellite-stable (MSS).

MSI and mutations

Among the 202 samples, nine MSI-H, 19 MSI-L, and 172 MSS were detected, whereas the MSI states of the remaining two samples could not be determined[25–28]. Two MSS samples were filtered out for all single-nucleotide variants under standard criteria (variation quality: PASS, location: exon, and mutation frequency > 0.01); thus, 200 samples were used for mutation-related analysis.

The tumor mutation burden (TMB) was calculated as the total number of somatic mutations divided by the capture size in Mb[29]. The TMB values in the MSI-H and MSI-L samples were significantly higher than those in the MSS samples (Wilcoxon rank-sum test, both $P < 0.01$) (Figure 1). The TMB values were 19.0 and 55.0 in the MSS and MSI samples, respectively, with an average of 52.5 and 56.1 for MSI-H and MSI-L, respectively. Nevertheless, no significant difference was noted in TMB values between the MSI-H and MSI-L groups[30,31]. The proportion of somatic point mutations in MSI samples was significantly higher than that in MSS samples, which is consistent with previous findings[32]. The increase in somatic mutations caused by MSI was not statistically significant according to pathological classification (Lauren classification) or clinical stage (TNM stage).

Nearly all patients harbored somatic mutations in the target area. The most commonly mutated gene was *TP53*, as previously discovered; however, the mutation rate of *TP53* was 33%, which is far lesser than that reported in other studies



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Figure 1 The distribution of tumor mutation burden in microsatellite instability-high, microsatellite instability-low, and microsatellite stable groups. Tumor mutation burden (TMB) in both microsatellite instability-high (MSI-H) and microsatellite instability-low (MSI-L) groups were higher than that in the microsatellite stable group ($p < 0.01$), whereas no difference was noted between the MSI-H and MSI-L groups. TMB: Tumor mutation burden; MSI-H: Microsatellite instability-high; MSI-L: Microsatellite instability-low; MSS: Microsatellite stable.

[23,26,27,33,34]. In total, 32 genes had mutation rates $> 10\%$, and 10 of these genes (including *KMT2B*, *SPEN*, and *LRP1B*) had mutation rates $> 20\%$ (Figure 2). Among the MSS and MSI samples, 31.8% (54/170) and 42.8% (12/28), respectively, had somatic mutations in *TP53*, whereas the difference was not significant between the groups ($P < 0.3$). Moreover, no obvious differences in the ratio of gene mutations were noted in the tumor differentiation levels or pathological types.

After co-analyzing the top 15 somatically mutated genes, *TP53* did not co-mutate with other genes but was exclusively mutated with *CDH1*. *TP53* was the most frequently mutated somatic protein in the GAC and modulated tumorigenesis. Co-analysis results suggested that *TP53* mutations may be a special molecular type that does not interact with other genes during GC occurrence (Figure 3). *CDH1* is an important gene associated with GAC. Therefore, further investigations were necessary because mutated *TP53* and *CDH1* may indicate two distinct patterns in the pathogenesis of GAC. Additionally, all genes, including *FAT1*, *MGA*, and *ZFH3*, were co-mutated, except for *TP53* and *CDH1*. Mutations in *TP53* and *CDH1* may present different patterns (Figure 4).

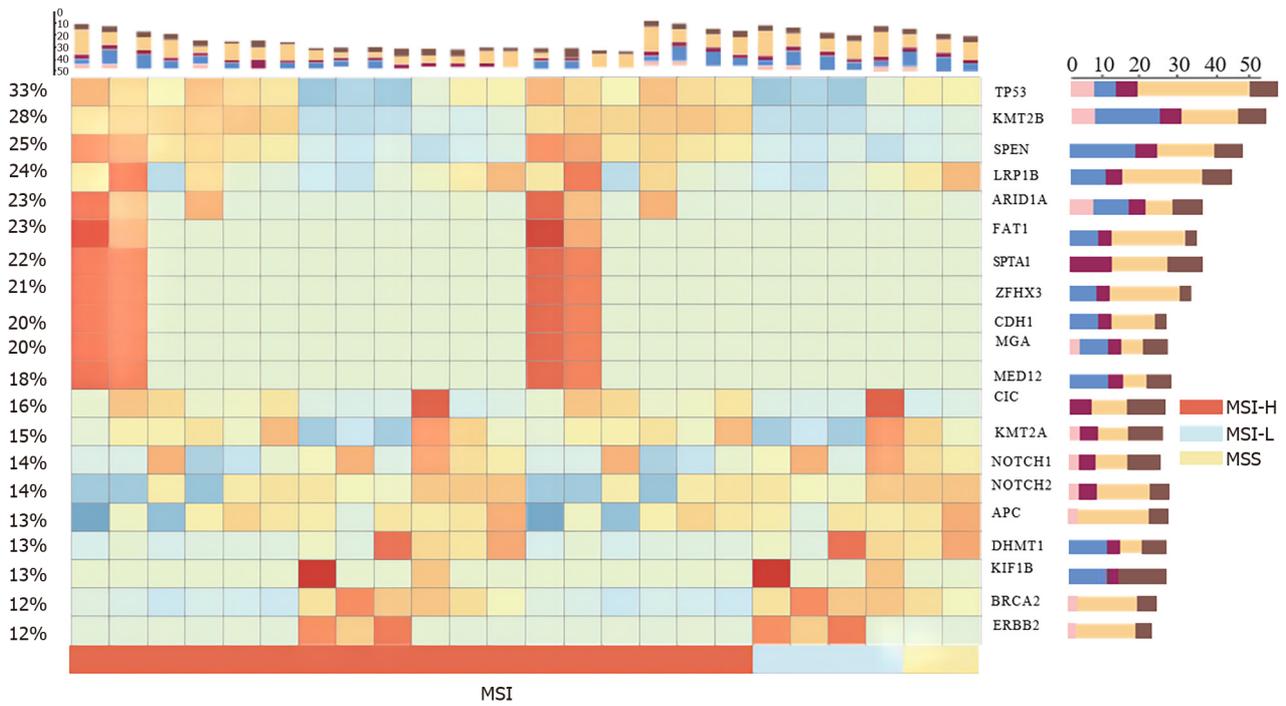
Driver genes

The driver genes were identified using OncodriveCLUST in maftools[35], followed by strict additional filtering criteria to focus on top driver genes (Figure 3). A total of 59 genes (false discovery rate < 0.05) were detected, of which only seven genes, including *KMT2B*, *SPEN*, *FAT1*, *MGA*, *MED12*, *KIF1B*, and *ERBB2*, overlapped with the top 20 somatically mutated genes. Most of the top driver genes, including *HOXB13*, *AKT3*, *CHEK1*, *FGFR3*, and *CALR*, were not included in the list of somatically mutated genes. Meanwhile, the top mutated genes, including *TP53* and *CDH1* were not important in the driver gene clusters because more regional clusters were identified based on the positions of the gene mutations. Low *HOXB13* expression is responsible for poor tumor differentiation, metastasis[36], and poor prognosis of GC. *AKT3*, which has a somatic mutation frequency of 7.5%, is an important driver gene. *AKT3* is an isoserine/threonine protein kinase that regulates *TP53* activity through acetylation. *CHEK1* (also known as *CHK1*), a gene involved in the DNA damage checkpoint pathway, cooperates with mismatch repair (MMR) deficiency to trigger chromosomal instability in MMR-deficient colorectal cancer cells[37]. Among the eight samples with *CHEK1* mutations, the numbers of MSI-H, MSI-L, and MSS were two, two, and four, respectively, which were significantly different from those in the whole cohort ($P < 0.05$). High *CALR* expression was observed in 20 of 30 patients with GC and was responsible for positive serosal invasion, lymph node metastasis, perineural invasion, and poor survival[38,39]; it is a good biomarker of prognosis in GC[40].

Survival analysis

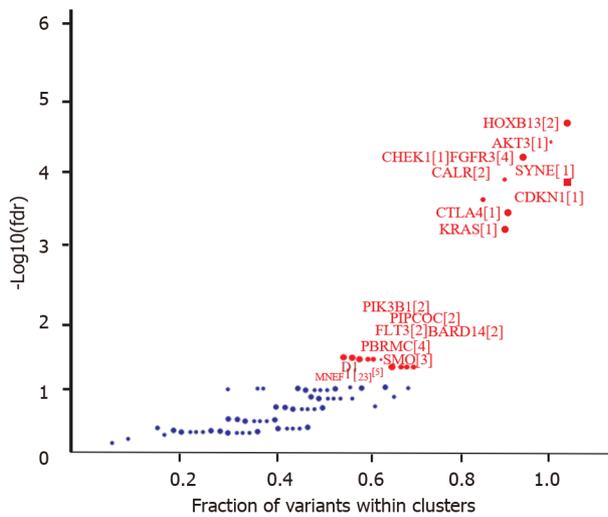
The OS of patients with MSS tumors was not significantly better than that of patients with MSI tumors ($P = 0.215$), whereas in patients with early GC (pT1), the OS of MSS was significantly longer than that of MSI ($P = 0.034$). The non-significant difference in OS between patients with MSI tumors and those with MSS tumors conflicts with the findings of previous reports. Several GC studies have suggested a positive relationship between MSI-H phenotype, mismatch repair deficiency, and better prognosis[41-43]. Although the outcome was not statistically significant, the survival analysis of 27 patients with stage IA suggested that patients with MSI tumors had a better prognosis than those with MSS tumors, whereas the MSS group had a better prognosis than patients with stage IB disease. Retrospective Asian studies confirmed the hypothesis that patients with MSS tumors benefit from adjuvant 5-fluorouracil-based chemotherapy, whereas those with MSI-H stage II or III GC do not[44-47]. Postoperative adjuvant chemotherapy was administered to patients with stage IB and advanced stages. Therefore, we speculated that adjuvant chemotherapy contributed to the differences in OS between patients with MSS and those with MSI at different stages.

Survival analysis revealed that somatic mutations in *TP53* were significantly correlated with a 5-year OS rate of 52.34% and a median survival time of 60.00 mo. Specifically, samples with *TP53* somatic mutations had a significantly lower 5-year OS rate than those without *TP53* somatic mutations (39% vs 58%, $P = 0.01$; Figure 5A). The samples were successfully classified based on pathological stage, and *TP53* did not affect the OS rate in the early (I/II) or middle-late (III/IV) stages (Figure 5B and C). Thus, the *TP53* mutation ratio was not associated with the pathological type, and a decrease in the OS rate was associated with a high mutation rate of *TP53* in middle-late stage cases. The mean OS rate of samples with *TP53*



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Figure 2 The mutation type and frequency of the top 20 mutated genes in samples clustered by microsatellite instability groups. *TP53* was the top mutated gene in gastric adenocarcinoma. MSI: Microsatellite instability; MSI-H: Microsatellite instability-high; MSI-L: Microsatellite instability-low; MSS: Microsatellite stable.

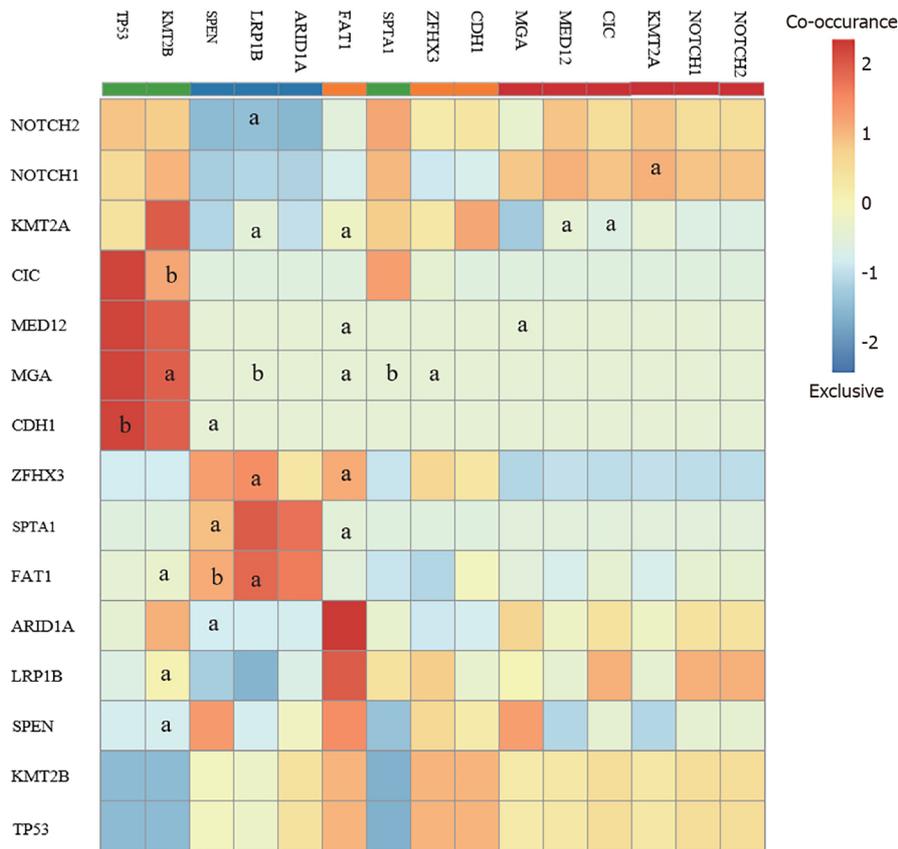


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Figure 3 Driver genes identified by OncodriveCLUST in maftools.

mutations was lower in diffuse GC than in those without *TP53* mutations (30.87 vs 37.49, Wilcoxon $P = 0.064$). In contrast, *CDH1* somatic mutations were not significantly associated with OS (63.83% vs 49.36%, $P = 0.33$; Figure 5D). Among patients without *TP53* mutations, those with *CDH1* mutations appeared to have higher survival rates; however, this difference was not significant. Moreover, those with both *TP53* and *CDH1* mutations had the worst 5-year OS rates ($P = 0.02$; Figure 5E). Nine patients had both *TP53* and *CDH1* mutations, of which one case had the highly differentiated intestinal type, whereas the other eight cases had Lauren diffuse GC.

Further investigation of the poorly differentiated diffuse cases led to the identification of 38 *TP53* and 36 *CDH1* mutations. Low-differentiation and diffuse GC had a higher percentage of *CDH1* somatic mutations, which was significantly different from other types of GC. Survival analysis revealed an overall poor prognosis in patients with poorly differentiated diffuse GC; the presence of *P53* mutations resulted in the worst prognosis, whereas that of *CDH1* had no significant effect.



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Figure 4 The co-occurrence and exclusion mutation relationships from the top 15 mutated genes in the samples. TP53 and CDH1 were exclusively mutated with $P < 0.1$, suggesting two different patterns in the pathogenesis of gastric adenocarcinoma. ^a $P < 0.05$; ^b $P < 0.1$.

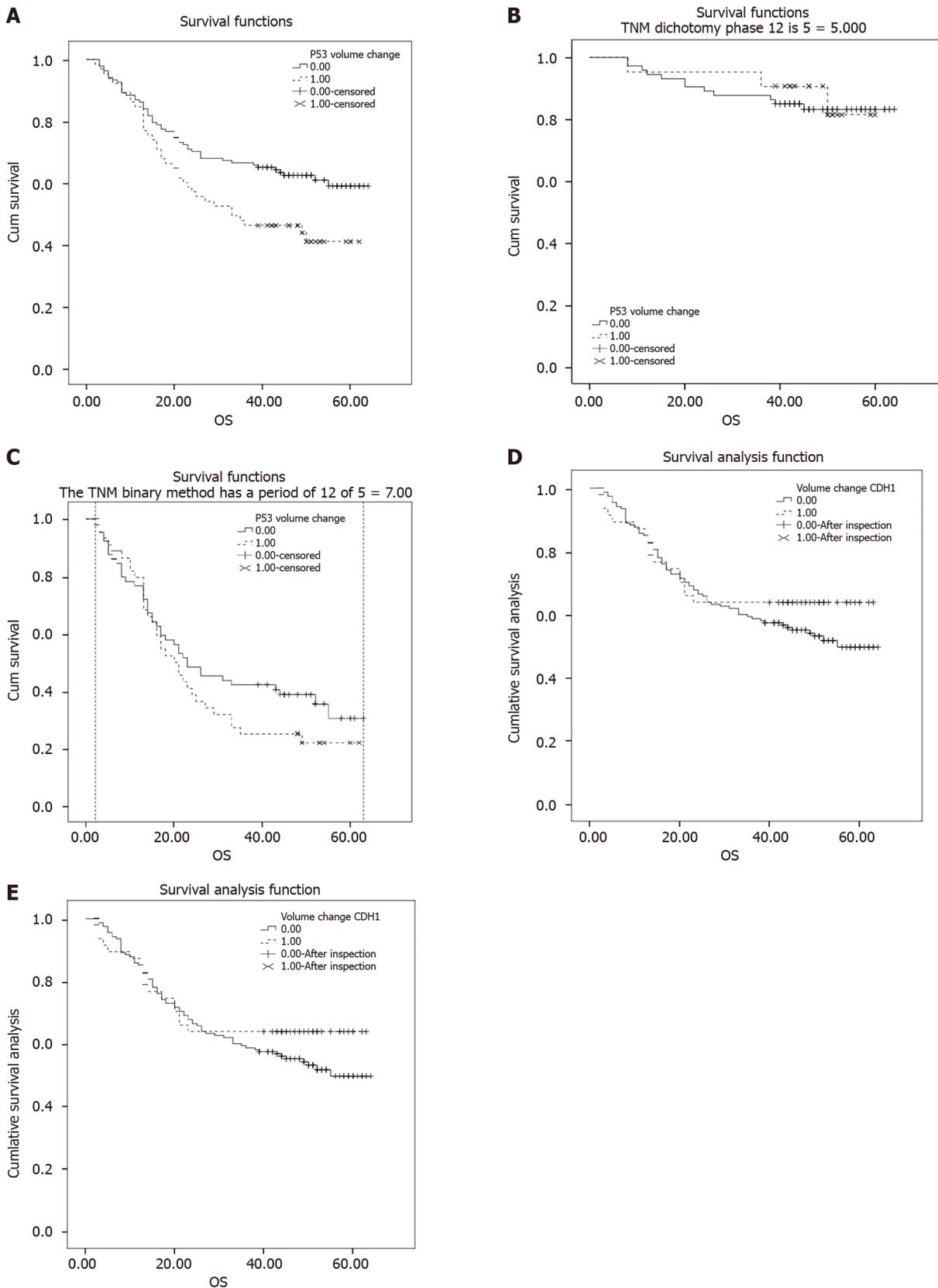
DISCUSSION

This study analyzed surgical cases between January 2014 and December 2015 at Xiangya Hospital and evaluated survival time after treatment. These results are similar to those of other epidemiological studies of GC in China. However, there is a lack of large-scale molecular genetic research on GC in China, because most existing studies have obtained specimens from Europe, America, Korea, and Vietnam. Our study revealed approximately 24.1 somatic mutations on average in the 1M capture area of GC samples, corroborating previous studies[23,26,27,33,34]. MSI is associated with a number of somatic mutations but may not be directly related to the pathological type and prognosis. The mutation frequencies of 32 genes, including TP53, KMT2B, SPEN, FAT1, and CDH1, in GC exceeded 10%. Our study provides molecular genetic data on Chinese patients with GC.

Our analysis of driver genes differed from that of previous studies in that TP53 and CDH1 were not identified as important driver genes. Driver gene mutations are typically increase the net cell growth under specific microenvironmental conditions in cells *in vivo*. TP53 and CDH1 did not co-mutate with other genes, showing unique biological features in GC samples.

Other studies have suggested that TP53, a crucial gene associated with GC development, has a somatic mutation rate of approximately 50%[27,33,34]. In this study, the overall mutation rate of TP53 was 33%; however, it was significantly higher in stages III/IV (41%) than in stages I/II (23%; $P < 0.01$). The mutation type of TP53 was consistent with that reported in previous studies[25-27], mainly single nucleotide mutations, such as C/T and T/C. Mutations located in exon 5 accounted for approximately 36% of all TP53 mutations, consistent with other studies, hence the overall lower TP53 mutation rate may be due to the composition of the clinical samples. Somatic mutations occur exclusively in TP53 and CDH1. TP53 did not co-mutate with other genes. Therefore, TP53 mutations may represent a unique type of GC tumorigenesis. Notably, the number and probability of lymph node metastases in patients with P53 mutations have increased, which may promote a high incidence of TP53 mutations in stage III/IV GC. Consequently, TP53 mutations modulate lymph node metastasis.

CDH1 is closely associated with GC and is the causative gene of diffuse hereditary lung cancer. In diffuse GC, the CDH1 mutation rate (25%) was higher than that in the non-diffuse type (11%; $P < 0.05$), which was consistent with previous findings. In contrast to TP53 mutations, CDH1 mutations play an important role in the development of diffuse GC through distinct mechanisms. As there is a clear connection between TP53 and tumor development, tumors with poor prognosis may be more likely to be in advanced stages. Although they have no direct effect on prognosis, the CDH1 mutation is a substantial contributor to diffuse GC. TP53 and CDH1 mutations may indicate two different types of GC at the molecular level, which warrants further investigation. The Cancer Genome Atlas had 23.5 mutations in this area[23].



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Figure 5 Survival analysis revealed that somatic mutations in TP53. A: Patients carrying the TP53 somatic mutation had significantly lower 5-year overall survival (OS) than those without the mutation; B and C: TP53 did not affect the OS rate in the early (I/II, B) or middle-late (III/IV, C) stages; D: CDH1 somatic mutation was not significantly related to the OS; E: Patients with both TP53 and CDH1 mutations had the worst 5-year OS rate. OS: Overall survival.

Moreover, the types and composition of mutations were similar to those reported in previous studies[26,27]. the results reported in previous studies[48,49].

CONCLUSION

GC is the third most common malignant tumor in China, and its incidence is much higher than that in Western countries. This study provides crucial molecular data on GC in Chinese patients because large-scale Chinese genetic evidence is lacking. This study revealed that *TP53* and *CDH1* mutations affect two important pathways in the occurrence and development of GC. The pathogenesis of GC in the Han Chinese population (in the middle and lower reaches of the Yangtze River), as well as the diagnosis and treatment of GC, would benefit from our findings. The proportion of MSI samples was consistent with that in previous research[30]. The prevalence of MSI-H GC in Asians is commonly < 10% of all GC cases[31], which is lower than most of the occurrence rates reported in Western studies.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is the third most common malignant tumor in China, and its incidence is much higher than that in Western countries. This study provides crucial molecular data on GC in Chinese patients because large-scale Chinese genetic evidence is lacking. This study revealed that *TP53* and *CDH1* mutations affect two important pathways in the occurrence and development of GC. The pathogenesis of GC in the Han Chinese population (in the middle and lower reaches of the Yangtze River), as well as the diagnosis and treatment of GC, would benefit from our findings.

Research motivation

One of the challenges to the design of effective treatments for GC is heterogeneity, its poses an obstacle for the uniform therapy plan irrespective of specific subtypes of tumors in clinical practice.

Research objectives

TP53 and *CDH1* have been reported to be closely related to GC; therefore, we aimed to investigate the clinical outcomes of *TP53* and *CDH1* mutations in GC.

Research methods

Two hundred and two primary GC tissues and matched non-cancerous (NC) tissues were sampled *via* surgery. After DNA extraction for cancer tissue and NC tissue, DNA was captured using customized panel from Roche NimbleGen Inc. The customized panel included the exons and hotspots of 490 genes with a total length of 1 Mb 10 sequencer (Illumina, Inc).

Research results

The mutation rates of 32 genes exceeded 10% including *TP53*, *SPEN*, *FAT1*, and *CDH1* *etc.* We found that *TP53* mutations had a slightly lower overall occurrence rate (33%), whereas the mutation type was similar to that reported in other studies. The *TP53* mutation rate was significantly higher in the advanced stages (stage III/IV) than that in the early stages (stage I/II) ($P < 0.05$). In contrast, we also found that *CDH1* mutation is significantly related to diffuse GC. *TP53* is related to the poor prognosis of advanced-stage tumors; nevertheless, *CDH1* corresponds to a diffuse type of cancer. Moreover, *TP53* was exclusively mutated to *CDH1*, which is the major reason for the two different GC mechanisms.

Research conclusions

Different somatic mutation patterns of *TP53* and *CDH1* indicate two major mechanisms underlying GC.

Research perspectives

Understanding the mutational landscape of *TP53* and *CDH1* would positively affect the pathogenesis of GC in the Han Chinese population (in the middle and lower reaches of the Yangtze River), as well as guiding the diagnosis and treatment of GC.

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FOOTNOTES

Co-first authors: He-Li Liu and Huan Peng.

Author contributions: Liu HL, Peng H, and Ge J designed the study; Huang CH collected and analyzed the clinical data; and Zhou HY wrote the paper; Liu HL and Peng H contributed equally to this work as co-first authors. The reasons for designating Liu HL and Peng H as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authors accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resulting paper. This also ensures the effective communication and management of post-submission matters, ultimately enhancing the quality and reliability of the paper. Second, the research team encompasses authors with a variety of expertise and skills from different fields, and the designation of co-first authors best reflects this diversity. This also promotes a more comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Liu HL and Peng H contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects their equal contribution, while recognizing the spirit of teamwork and collaboration in this study. In summary, we believe that designating Liu HL and Peng H as co-first authors fits our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity. All authors approved the final version of the article.

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Country/Territory of origin: China

ORCID number: He-Li Liu 0000-0002-3443-6174; Huan Peng 0000-0002-3073-5708; Chang-Hao Huang 0009-0000-6755-6618; Hai-Yan Zhou 0000-0002-2860-1858; Jie Ge 0000-0002-4186-4740.

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