Clinicopathological Characteristics, Survival Outcomes, and Genetic Alterations of Younger Patient With Gastric Cancer: Results From China National Cancer Center and cBioPortal

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Research Article

Keywords: Gastric cancer, Younger patient, Clinicopathological characteristics, Survival outcomes, Genetic alterations

Posted Date: September 7th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-862005/v1>

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Version of Record: A version of this preprint was published at Cancer Medicine on March 22nd, 2022. See the published version at <https://doi.org/10.1002/cam4.4669>.

Abstract

Background

Survival outcomes of younger patients with gastric cancer (GC) remains controversial. The present study sought to explore clinicopathological characteristics, survival outcomes, and genetic alterations in the younger and older patients with GC.

Methods

Patients with GC were identified from the China National Cancer Center Gastric Cancer Database (NCCGCDB) during 1998–2018. Survival analysis was conducted via Kaplan-Meier estimates and Cox proportional hazards models. Sequencing data were enrolled from the China National Cancer Center, TCGA, and MSKCC databases.

Results

A total of 1146 younger and 16988 older cases were included. Patients in the younger group were predominant in poor differentiation (53.7% versus 33.8%, $P<0.0001$), and pTNM stage IV (19.5% versus 11.8%, $P<0.001$). The 5-year overall survival (OS) of patients in NCCGCDB has noticeable increased from 1998 to 2018. Younger age was an independent prognostic factor for GC patients in pTNM stage III ($P=0.014$), while other stages showed no difference. Compared to the younger, older patients had a higher mutation frequency in *LRP1B*, *GNAS*, *APC*, *KMT2D* genes (all $P<0.05$). In addition, although no significant difference, results of the China National Cancer Center, TCGA, and MSKCC cohorts indicated that younger patients dominated in *CDH1*, *RHOA*, and *CTNNB1* mutations.

Conclusions

Stable proportion of younger cases and noticeable survival improvements were reported in the China National Cancer Center. Younger patients with pTNM stage III had a worse survival than older, while other tumor stages showed no difference. Furthermore, distinctive molecular characteristics were identified in younger GC patients, which might partly explain histopathological behaviors and prognosis of in this subpopulation.

Background

Gastric cancer (GC) remained one of the most frequent digestive cancers and represented the fourth leading cause of cancer-related death worldwide [1]. More than 40 % of GC cases and deaths occurred in China, with an age-standardized 5-year survival rate of 35.1% [2, 3, 4]. It was generally considered that GC mostly onset in patients aged 50–70 years, and younger patients only account for 2.0-6.2% [5, 6]. Although the incidence of GC revealed a decline in the general population, concern has been raised about the stable or increased trends of younger patients in the last decades [7, 8, 9].

Younger patients with GC were more likely to exhibit distinctive biological behaviors, such as female predominance, poor differentiation, and advanced stage [10–13]. To date, results for the survival outcomes in younger patients with GC have been inconsistent [10–15]. Some studies reported that younger patients own a longer survival time than older [10, 11], whereas others showed no difference [12, 13]. Several studies even revealed poor survival of GC in younger adults [14, 15]. From the molecular perspective, the increased incidence of younger patients might owe to the distinctive pathogenesis, and certain genetic alterations have been demonstrated to play a critical role in the progression and prognosis of GC among age groups [16, 17]. However, recent knowledge regarding the mutation profiles in younger GC patients was limited, and a comprehensive molecular profile target younger patients should be defined to enhance understanding of molecular pathology in this subpopulation.

In this study, we sought to explore trends of clinicopathological characteristics and survival outcomes in younger and older patients from the China National Cancer Center over the past 20 years, which might serve as a reference for a large population-based study in China. Moreover, genetic alterations of younger patients were comprehensively investigated based on the China National Cancer Center and the cBioPortal for Cancer Genomics database, thus providing novel insights for the genomics and precision medicine of this subpopulation.

Methods

Data source and patient selection

The study population was described in detail in the previous research [18, 19]. Briefly, all histologically confirmed incident cases of GC diagnosed between 1998 and 2018 in the cancer center were identified through the China National Cancer Center Gastric Cancer Database (NCCGCDB). Enrollment criteria included age between 18 and 85 years, residence in China, and without a previous cancer diagnosis, except for GC. All GC cases that met the inclusion criteria were divided into two age groups: the younger group (<40 years of age) and older group (≥ 40 years of age). The rationale for younger group was to remain consistent with the majority of prior studies [11, 20, 21]. Clinical data abstracted from the NCCGCDB included patients' demographics, clinicopathological characteristics, and survival variables. Stage of GC was assessed according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. The primary endpoints of the study were OS and progression-free survival (PFS). According to the time of histological diagnosis, changing trends of the younger and older patients with GC were investigated in four consecutive periods: from 1998 to 2003 (period 1), from 2003 to 2008 (period 2), from 2008 to 2013 (period 3), and from 2013 to 2018 (period 4).

Of 29 patients with GC included in the further molecular analysis had their tumor specimens sequenced at our institution. All tumor samples were evaluated by pathologists prior to DNA extraction for sequencing. Moreover, we searched the online cBioPortal for Cancer Genomics (<http://www.cbioportal.org/>) to obtain high-volume genetic resources [19–22]. Finally, 8 gastric adenocarcinoma datasets from TCGA and MSKCC databases met our inclusion criteria, and a total of 1098 GC cases with clear clinical data and mutation detection by next-generation sequencing (NGS) were included in the comparative analysis.

DNA extraction and sequencing

DNA from tumor samples and peripheral blood was extracted via the QIAamp DNA Mini Kit (QIAGEN, Valencia, CA) according to the manufacturer's instructions. Qubit's DNA assay was performed to measure the DNA concentration. A minimum of 50 ng of DNA is required for construction of an NGS library. For GC patients with available DNA, targeted DNA sequencing was performed. DNA was profiled by using a capture-based targeted sequencing panel (Burning Rock Biotech, Guangzhou, People's Republic of China), targeting 520 genes and spanning 1.67M of Human genomic regions.

Sequencing data analysis

Sequencing data were mapped to the human genome (hg19) using BWA aligner 0.7.10. Local alignment optimization and variant calling were performed using GATK v3.2-2, while DNA translocation analysis was performed using both Tophat2 and Factera 1.4.3. Different mutation calling thresholds were applied on samples with different DNA qualities to avoid false-positive mutation calls due to DNA damage. Single nucleotide variants (SNVs) and insertion-deletions (INDELs) indels identified were annotated using the dbNSFP(v30a), COSMIC (v69), and dbSNP (snp138) database. Variants with a global minor allele frequency greater than 1.0% in 1000Genome Project (Phase3, <http://www.1000genomes.org/data>) were considered as common SNPs and removed. Tumor mutational burden (TMB) was defined as the number of somatic, coding, base substitution, and indels per megabase of genome examined. Synonymous mutations were counted to reduce sampling noise. White blood cells were used to filter germline mutations.

Statistical Analysis

The bar chart was plotted to evaluate the variation in tumor stage for younger and older patients from 1998 to 2018. The Chi-squared test was performed to compare categorical variables between the two groups, while continuous variables were evaluated using Student's t-test. OS and PFS for the younger and older group were calculated with the Kaplan-Meier method, while the log-rank test estimated the relevant survival discrepancy. Associations between risk factors and OS were investigated by univariate and multivariate Cox proportional hazard regression analysis, while the corresponding hazard ratio (HR) and 95% CI were generated. The covariates included in the final models were determined by using stepwise selection with minimized AIC. The significant level for adding variables was 0.05, and the significance level for removing variables was 0.10. Statistical significance was set at two-sided P values less than 0.05, and all analyses in the study were conducted using SAS software v9.4 (SAS Institute, Inc., Cary, NC).

Results

Demographic and Clinicopathological features

From 1998 to 2018, a total of 1146 younger cases (6.3%) and 16988 older cases (93.7%) were finally included. Among all GC patients, 2035 were diagnosed in period 1, 3859 in period 2, 6054 in period 3, and 6150 in period 4 (As shown in Table 1). There were significant differences in the distribution of gender, smoking, alcohol history, BMI, primary tumor location, differentiation, pTNM stage between the younger group and older group (all $P < 0.01$). Distinctive demographic disparities among age groups were founded in the China National Cancer Center. Younger patients were predominant in females (50.1% versus 21.6%, $P < 0.0001$). Conversely, relatively higher percentages of smokers (21.1% versus 42.4%, $P < 0.0001$), alcohol drinkers (20.9% versus 34.5%, $P < 0.0001$), and overweight/obesity ($BMI \geq 23$) (36.1% versus 53.4%, $P < 0.0001$) were revealed in older.

Table 1

Demographic and clinicopathological characteristics between younger group and older group in 4 consecutive periods (bidirectional cohort 1998-2018).

	Period 1 (1998-2003)			Period 2 (2004-2008)			Period 3 (2009-2013)			Period 4 (2014-2018)		
	Younger group	Older group	P Value	Younger group	Older group	P Value	Younger group	Older group	P Value	Younger group	Older group	P Value
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)				
Gender												
Male	83 (50.0%)	1,367 (73.14%)	<0.0001	112 (46.1%)	2,744 (75.1%)	<0.0001	209 (52.6%)	4,321 (76.4%)	<0.0001	168 (49.4%)	4,384 (75.5%)	<0.0001
Female	83 (50.0%)	502 (26.86%)		131 (53.9%)	908 (24.9%)		188 (47.4%)	1,336 (23.6%)		172 (50.6%)	1,426 (24.5%)	
Smoking history												
No	132 (79.5%)	1,180 (63.1%)	0.0001	195 (80.3%)	2,242 (61.4%)	<0.0001	302 (76.1%)	3,110 (55.0%)	<0.0001	241 (70.9%)	2,813 (48.4%)	<0.0001
Yes	33 (19.9%)	670 (35.9%)		39 (16.1%)	1,247 (34.2%)		84 (21.2%)	2,393 (42.3%)		86 (25.3%)	2,896 (49.9%)	
Unknown	1 (0.6%)	19 (1.0%)		9 (3.7%)	163 (4.5%)		11 (2.8%)	154 (2.7%)		13 (3.8%)	101 (1.7%)	
Drinking history												
No	131 (78.9%)	1,328 (71.1%)	0.095	206 (84.8%)	2,562 (70.2%)	<0.0001	304 (76.6%)	3,594 (63.5%)	<0.0001	230 (67.7%)	3,190 (54.9%)	<0.0001
Yes	34 (20.5%)	520 (27.8%)		27 (11.1%)	919 (25.2%)		81 (20.4%)	1,908 (33.7%)		97 (28.5%)	2,519 (43.4%)	
Unknown	1 (0.6%)	21 (1.1%)		10 (4.1%)	171 (4.7%)		12 (3.0%)	155 (2.7%)		13 (3.8%)	101 (1.7%)	
BMI (kg/m ²) at diagnosis												
<18.5	29 (17.5%)	124 (6.6%)	<0.0001	50 (20.6%)	264 (7.2%)	<0.0001	52 (13.1%)	336 (5.9%)	<0.0001	54 (15.9%)	283 (4.9%)	<0.0001
18.5-22.9	73 (44.0%)	733 (39.2%)		109 (44.9%)	1,346 (36.9%)		182 (45.8%)	2,162 (38.2%)		143 (42.1%)	2,101 (36.2%)	
23-27.4	48 (28.9%)	755 (40.4%)		53 (21.8%)	1,388 (38.0%)		110 (27.7%)	2,262 (40.0%)		98 (28.8%)	2,574 (44.3%)	
≥27.5	9 (5.4%)	196 (10.5%)		17 (7.0%)	423 (11.6%)		39 (9.8%)	701 (12.4%)		40 (11.8%)	766 (13.2%)	
Unknown	7 (4.2%)	61 (3.3%)		14 (5.8%)	231 (6.3%)		14 (3.5%)	196 (3.5%)		5 (1.5%)	86 (1.5%)	
Weight loss												
None	61 (36.8%)	615 (32.9%)	0.022	104 (42.8%)	1,427 (39.1%)	0.66	241 (60.7%)	3,238 (57.2%)	0.086	209 (61.5%)	3,504 (60.3%)	0.0001
<10%	44 (26.5%)	461 (24.7%)		50 (20.6%)	842 (23.1%)		78 (19.7%)	1,419 (25.1%)		74 (21.8%)	1,531 (26.4%)	
≥10%	25 (15.1%)	191 (10.2%)		23 (9.5%)	339 (9.3%)		46 (11.6%)	547 (9.7%)		37 (10.9%)	557 (9.6%)	
Unknown	36 (22.7%)	602 (32.2%)		66 (27.2%)	1,044 (28.6%)		32 (8.1%)	453 (8.0%)		20 (5.9%)	218 (3.8%)	
H. pylori infection												
Negative	0 (0.0%)	3 (0.2%)	1.00	1 (0.4%)	51 (1.4%)	0.50	23 (5.8%)	397 (7.0%)	0.64	59 (17.4%)	1,004 (17.3%)	0.7
Positive	0 (0.0%)	11 (0.6%)		2 (0.8%)	42 (1.2%)		38 (9.6%)	522 (9.2%)		27 (7.9%)	524 (9.0%)	
Unknown	166 (100.0%)	1,855 (99.3%)		240 (98.8%)	3,559 (97.5%)		336 (84.6%)	4,738 (83.8%)		254 (74.7%)	4,282 (73.7%)	
Primary tumor location												
Proximal	28 (16.9%)	836 (44.7%)		32 (13.2%)	1,403 (38.4%)		65 (16.4%)	2,164 (38.3%)		49 (14.4%)	2,115 (36.4%)	

Distal	126 (75.9%)	898 (48.1%)		198 (81.5%)	1,996 (54.7%)		296 (74.6%)	3,082 (54.5%)		265 (77.9%)	3,105 (53.4%)	
Overlapping lesions	6 (3.6%)	85 (4.6%)		3 (1.2%)	94 (2.6%)		19 (4.8%)	250 (4.4%)		15 (4.4%)	422 (7.3%)	
Unknown	6 (3.6%)	50 (2.7%)	<0.0001	10 (4.1%)	159 (4.4%)	<0.0001	17 (4.3%)	161 (2.9%)	<0.0001	11 (3.2%)	168 (2.9%)	<0.
Lauren classification												
Intestinal	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (0.0%)		16 (4.0%)	1,073 (19.0%)		23 (6.8%)	1,724 (29.7%)	
Diffuse	0 (0.0%)	1 (0.1%)		0 (0.0%)	1 (0.0%)		111 (28.0%)	942 (16.7%)		173 (50.9%)	1,380 (23.8%)	
Mixed	0 (0.0%)	1 (0.1%)		0 (0.0%)	4 (0.1%)		25 (6.3%)	607 (10.7%)		47 (13.8%)	1,115 (19.2%)	
Unknown	166 (100.0%)	1,867 (99.9%)	1.00	243 (100.0%)	3,646 (99.8%)	1.00	245 (61.7%)	3,035 (53.7%)	<0.0001	97 (28.5%)	1,591 (27.4%)	<0.
Borrmann classification												
Borrmann I	13 (7.8%)	210 (11.2%)		6 (2.5%)	316 (8.7%)		30 (7.6%)	537 (9.5%)		29 (8.5%)	587 (10.1%)	
Borrmann II	45 (27.1%)	750 (40.1%)		96 (39.5%)	1,327 (36.3%)		134 (33.8%)	2,115 (37.4%)		107 (31.5%)	2,085 (35.9%)	
Borrmann III	52 (31.3%)	400 (21.4%)		52 (21.4%)	859 (23.5%)		87 (21.9%)	1,304 (23.1%)		93 (27.4%)	1,666 (28.7%)	
Borrmann IV	16 (9.6%)	116 (6.2%)		23 (9.5%)	306 (8.4%)		37 (9.3%)	316 (5.6%)		20 (5.9%)	250 (4.3%)	
Mixed	2 (1.2%)	7 (0.4%)		0 (0.0%)	9 (0.3%)		1 (0.3%)	12 (0.2%)		11 (3.2%)	150 (2.6%)	
Unknown	38 (22.9%)	386 (20.7%)	0.0010	66 (27.2%)	835 (22.9%)	0.014	108 (27.2%)	1,373 (24.3%)	0.022	80 (23.5%)	1,072 (18.5%)	0.0
Linitis plastica												
No	162 (97.6%)	1,851 (99.0%)		232 (95.5%)	3,474 (95.1%)		359 (90.4%)	5,312 (93.9%)		321 (94.4%)	5,565 (95.8%)	
Yes	4 (2.4%)	9 (0.5%)		1 (0.4%)	13 (0.4%)		13 (3.3%)	57 (1.0%)		11 (3.2%)	72 (1.2%)	
Unknown	0 (0.0%)	9 (0.5%)	0.028	10 (4.1%)	165 (4.5%)	0.95	25 (6.3%)	288 (5.1%)	0.0001	8 (2.4%)	173 (3.0%)	0.0
Differentiation												
Well	1 (0.6%)	44 (2.4%)		0 (0.0%)	60 (1.6%)		4 (1.0%)	126 (2.2%)		1 (0.3%)	130 (2.2%)	
Moderate	21 (12.7%)	658 (35.2%)		26 (10.7%)	1,162 (31.8%)		34 (8.6%)	1,882 (33.3%)		42 (12.4%)	2,167 (37.3%)	
Poor	87 (52.4%)	575 (30.8%)		116 (47.7%)	1,179 (32.3%)		216 (54.4%)	1,931 (34.1%)		196 (57.7%)	2,054 (35.4%)	
Undifferentiated	0 (0.0%)	1 (0.1%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	2 (0.0%)		0 (0.0%)	1 (0.0%)	
Unknown	57 (34.3%)	591 (31.6%)	<0.0001	101 (41.6%)	1,251 (34.3%)	<0.0001	143 (36.0%)	1,716 (30.3%)	<0.0001	101 (29.7%)	1,458 (25.1%)	<0.
HER2 score												
0 (-)	1 (0.6%)	0 (0.0%)		3 (1.2%)	19 (0.5%)		90 (22.7%)	1,231 (21.8%)		120 (35.3%)	2,020 (34.8%)	
1 (+)	0 (0.0%)	1 (0.1%)		0 (0.0%)	3 (0.1%)		96 (24.2%)	1,291 (22.8%)		107 (31.5%)	1,523 (26.2%)	
2 (++)	0 (0.0%)	1 (0.1%)		0 (0.0%)	3 (0.1%)		27 (6.8%)	531 (9.4%)		19 (5.6%)	673 (11.6%)	
3 (+++)	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (0.0%)		12 (3.0%)	293 (5.2%)		7 (2.1%)	288 (5.0%)	
Unknown	165 (99.4%)	1,867 (99.9%)	0.23	240 (98.8%)	3,626 (99.3%)	0.46	172 (43.3%)	2,311 (40.9%)	0.13	87 (25.6%)	1,306 (22.5%)	0.0

Pathologic T-stage												
T0+Tis	0 (0.0%)	1 (0.1%)		2 (0.8%)	13 (0.4%)		1 (0.3%)	20 (0.4%)		0 (0.0%)	24 (0.4%)	
T1	17 (10.2%)	159 (8.5%)		37 (15.2%)	357 (9.8%)		59 (14.9%)	796 (14.1%)		81 (23.8%)	1,269 (21.8%)	
T2	13 (7.8%)	135 (7.2%)		15 (6.2%)	248 (6.8%)		30 (7.6%)	491 (8.7%)		36 (10.6%)	554 (9.5%)	
T3	2 (1.2%)	13 (0.7%)		22 (9.1%)	311 (8.5%)		80 (20.2%)	1,712 (30.3%)		39 (11.5%)	1,159 (20.0%)	
T4	98 (59.0%)	1,156 (61.9%)		110 (45.3%)	1,903 (52.1%)		116 (29.2%)	1,374 (24.3%)		114 (33.5%)	1,654 (28.5%)	
TX	36 (21.7%)	405 (21.7%)	0.74	57 (23.5%)	820 (22.5%)	0.066	111 (28.0%)	1,264 (22.3%)	0.0004	70 (20.6%)	1,150 (19.8%)	0.0
Pathologic N-stage												
N0	27 (16.3%)	418 (22.4%)		62 (25.5%)	830 (22.7%)		97 (24.4%)	1,518 (26.8%)		110 (32.4%)	1,893 (32.6%)	
N1	21 (12.7%)	273 (14.6%)		31 (12.8%)	520 (14.2%)		41 (10.3%)	775 (13.7%)		31 (9.1%)	729 (12.6%)	
N2	29 (17.5%)	310 (16.6%)		24 (9.9%)	510 (14.0%)		52 (13.1%)	797 (14.1%)		55 (16.2%)	766 (13.2%)	
N3	50 (30.1%)	459 (24.6%)		64 (25.3%)	888 (24.3%)		91 (22.9%)	1,222 (21.6%)		70 (20.6%)	1,195 (20.6%)	
NX	39 (23.5%)	409 (21.9%)	0.27	62 (25.5%)	904 (24.8%)	0.36	116 (29.2%)	1,345 (23.8%)	0.060	74 (21.8%)	1,227 (21.1%)	0.2
Pathologic M-stage												
M0	122 (73.5%)	1,563 (83.6%)		178 (73.3%)	2,939 (80.5%)		284 (71.5%)	4,517 (79.9%)		266 (78.2%)	4,882 (84.0%)	
M1	40 (24.1%)	261 (14.0%)		48 (19.8%)	430 (11.8%)		81 (20.4%)	714 (12.6%)		54 (15.9%)	601 (10.3%)	
MX	4 (2.4%)	45 (2.4%)	0.0020	17 (7.0%)	283 (7.8%)	0.0012	32 (8.1%)	426 (7.5%)	<0.0001	20 (5.9%)	327 (5.6%)	0.0
pTNM stage												
0	0 (0.0%)	1 (0.1%)		2 (0.8%)	12 (0.3%)		1 (0.3%)	20 (0.4%)		0 (0.0%)	19 (0.3%)	
I	17 (10.2%)	210 (11.2%)		42 (17.3%)	470 (12.9%)		71 (17.9%)	1,010 (17.9%)		94 (27.7%)	1,422 (24.5%)	
II	10 (6.0%)	63 (3.4%)		24 (9.9%)	279 (7.6%)		40 (10.1%)	948 (16.8%)		34 (10.0%)	935 (16.1%)	
III	85 (51.2%)	1,103 (59.0%)		99 (40.7%)	1,895 (51.9%)		153 (38.5%)	2,182 (38.6%)		128 (37.7%)	2,048 (35.3%)	
IV	40 (24.1%)	261 (14.0%)		48 (19.8%)	430 (11.8%)		81 (20.4%)	714 (12.6%)		54 (15.9%)	601 (10.3%)	
Unknown	14 (8.4%)	231 (12.4%)	0.0039	28 (11.5%)	566 (15.5%)	<0.0001	51 (12.9%)	783 (13.8%)	<0.0001	30 (8.8%)	785 (13.5%)	0.0
Lymphatic invasion												
No	76 (45.8%)	986 (52.8%)		123 (50.6%)	1,777 (48.7%)		183 (46.1%)	2,830 (50.0%)		152 (44.7%)	2,384 (41.0%)	
Yes	36 (21.7%)	357 (19.1%)		34 (14.0%)	749 (20.5%)		75 (18.9%)	1,182 (20.9%)		82 (24.1%)	1,959 (33.7%)	
Unknown	54 (32.5%)	526 (28.1%)	0.23	86 (35.4%)	1,126 (30.8%)	0.039	139 (35.0%)	1,645 (29.1%)	0.043	106 (31.2%)	1,467 (25.3%)	0.0
Vascular invasion												
No	76 (45.8%)	988 (52.9%)		124 (51.0%)	1,776 (48.6%)		183 (46.1%)	2,828 (50.0%)		152 (44.7%)	2,375 (40.9%)	
Yes	36 (21.7%)	354 (18.9%)		34 (14.0%)	742 (20.3%)		74 (18.6%)	1,185 (21.0%)		82 (24.1%)	1,973 (34.0%)	

Unknown	54 (32.5%)	527 (28.2%)	0.22	85 (35.0%)	1,134 (31.1%)	0.051	140 (35.3%)	1,644 (29.1%)	0.031	106 (31.2%)	1,462 (25.2%)	0.0
Nerve invasion												
No	110 (66.3%)	1,330 (71.2%)		153 (63.0%)	2,427 (66.5%)		186 (46.9%)	3,094 (54.7%)		117 (34.4%)	2,120 (36.5%)	
Yes	2 (1.2%)	13 (0.7%)		5 (2.1%)	100 (2.7%)		69 (17.4%)	917 (16.2%)		122 (35.9%)	2,321 (40.0%)	
Unknown	54 (32.5%)	526 (28.1%)	0.35	85 (35.0%)	1,125 (30.8%)	0.35	142 (35.8%)	1,646 (29.1%)	0.0064	101 (29.7%)	1,369 (23.6%)	0.0
Therapeutic regimen												
Surgery only	3 (1.8%)	99 (5.3%)		12 (4.9%)	149 (4.1%)		19 (4.8%)	347 (6.1%)		55 (16.2%)	871 (15.0%)	
Multimodality treatment	54 (32.5%)	452 (24.2%)		72 (29.6%)	908 (24.9%)		166 (41.8%)	1,800 (31.8%)		149 (43.8%)	2,052 (35.3%)	
Unknown	109 (65.7%)	1,318 (70.5%)	0.014	159 (65.4%)	2,595 (71.1%)	0.18	212 (53.4%)	3,510 (62.1%)	0.0002	136 (40.0%)	2,887 (49.7%)	0.0
Surgical margin												
Negative	120 (72.3%)	1,355 (72.5%)		173 (71.2%)	2,650 (72.6%)		265 (66.8%)	4,110 (72.7%)		251 (73.8%)	4,417 (76.0%)	
Positive	11 (6.6%)	110 (5.9%)	0.92	4 (1.7%)	103 (2.8%)	0.41	8 (2.0%)	106 (1.9%)	0.037	7 (2.1%)	92 (1.6%)	0.5

As for tumor, younger patients were more common in distal location (77.2% versus 53.5%, $P < 0.0001$), Borrmann IV (8.4% versus 5.8%, $P < 0.05$), poor differentiation (53.7% versus 33.8%, $P < 0.0001$), and pTNM stage IV (19.5% versus 11.8%, $P < 0.001$). The percentage of negative surgical margin in the patients aged ≥ 40 was higher than that in younger patients, but there were no significant statistical differences in all four periods (all $P \geq 0.05$). Among patients in period 3 and period 4, GC in the younger group was more likely to present with diffuse classification ($P < 0.0001$), and also had more lymphatic invasion and vascular invasion ($P = 0.043$, $P = 0.0008$, $P = 0.031$, $P = 0.0006$, resp.). In period 1, period 3 and period 4, younger patients with GC also demonstrated a better acceptance of multimodality treatment (32.5% versus 24.2%, $P = 0.014$; 41.8% versus 31.8%, $P < 0.001$; 43.8% versus 35.3%, $P = 0.0016$).

Trends of clinicopathological features of younger patients with GC over the past 20 years were investigated. The median proportion of patients in the younger group over time was 6.2% (range 5.5–8.2%). No trend for the proportion of young patients from period 2 to period 4 was noted on linear regression ($P = 0.053$). The proportion of HER2 score of 0(-) and 1(+) had increased from period 3 to period 4 (22.7–35.3%, 24.2–31.5%, resp.), while the score of 2(++) and 3(+++) showed downward trends (6.8–5.6%, 3.0–2.1%, resp.). As shown in Fig. 1, the percentages of pTNM tumor stage I and pTNM stage II in the younger group had increased gradually with time (from 10.2% in period 1 to 22.7% in period 4, from 6.0% in period 1 to 10.0% in period 4, resp.), whereas GC in pTNM stage III and pTNM stage IV showed a decrease (from 51.2% in period 1 to 37.7% in period 4, from 24.1% in period 1 to 15.9% in period 4, resp.). In the therapeutic regimen, both the percentages of younger patients undergoing surgery and the patients after multimodality treatment had increased from period 1 to period 4 (1.8–16.2%, 32.5–42.8%, resp.). As for surgical margin, a significant decrease was observed in positive margin for the younger group during 20 years. (from 6.6% in period 1 to 2.1% in period 4).

OS and PFS for younger patients with GC

Changing trends of OS and PFS between younger and older groups were shown in Table 2 and Fig. 2. In general, a noticeable survival increment of GC was demonstrated in Cancer Center during 20 years. The 5-year OS in younger and older group has increased from 44.4% (95%CI: 28.2%–60.7%) to 86.0% (95%CI: 81.7%–90.4%) and from 40.4% (95%CI: 36.0%–44.8%) to 86.3% (95%CI: 85.2%–87.4%), respectively. After stratification by pTNM stage, the increased survival of younger cases was pronounced in stages III and IV (31.3% in period 1 to 83.6% in period 4, 0% in period 1 to 55.5% in period 4, resp.). Moreover, the 5-year PFS of younger patients has increased from 17.1% (95%CI: 8.3%–26.0%) in period 1 to 65.5% (95%CI: 58.4%–72.6%) in period 4, with an obvious dominance in pTNM stage III (8.1–62%).

Table 2

The 5-year overall and progression-free survival rates by cancer stages (bidirectional cohort 1998-2018).

Survival analysis	Total, % (95% CI)	pTNM stage I, % (95% CI)	pTNM stage II, % (95% CI)	pTNM stage III, % (95% CI)	pTNM stage IV, % (95% CI)
Total					
Overall survival					
Total (n = 13,533)	68.1 (67.2-68.9)	96.6 (95.8-97.3)	85.1 (83.3-86.8)	61.8 (60.4-63.2)	19.0 (16.3-21.8)
Younger (n = 837)	61.8 (58.2-65.4)	99.5 (98.5-100.0)	80.6 (71.6-89.5)	55.1 (49.0-61.2)	16.2 (8.4-24.0)
Older (n = 12,696)	68.5 (67.6-69.4)	96.3 (95.5-97.1)	85.3 (83.5-87.0)	62.3 (60.8-63.7)	19.4 (16.5-22.4)
Progression-free survival					
Total (n = 12,728)	53.4 (52.4-54.3)	90.4 (89.1-91.7)	75.4 (73.2-77.5)	46.8 (45.4-48.2)	8.5 (6.6-10.4)
Younger (n = 856)	46.0 (42.4-49.6)	95.6 (92.4-98.8)	63.1 (52.2-74.1)	36.3 (30.7-42.0)	8.7 (3.6-13.8)
Older (n = 11,872)	53.9 (53.0-54.9)	89.9 (88.6-91.3)	76.0 (73.9-78.2)	47.5 (46.0-49.0)	8.4 (6.3-10.4)
Period 1					
Overall survival					
Total (n = 511)	40.7 (36.4-45.0)	94.0 (88.9-99.1)	78.3 (61.4-95.1)	32.4 (26.9-37.8)	4.8 (0.0-10.2)
Younger (n = 36)	44.4 (28.2-60.7)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	31.3 (8.5-54.0)	0.0 (0.0-0.0)
Older (n = 475)	40.4 (36.0-44.8)	93.3 (87.7-99.0)	75.0 (56.0-94.0)	32.5 (26.8-38.1)	5.4 (0.0-11.3)
Progression-free survival					
Total (n = 794)	26.5 (23.4-29.5)	79.8 (71.9-87.7)	42.4 (25.6-59.3)	21.7 (17.9-25.4)	2.2 (0.0-5.1)
Younger (n = 70)	17.1 (8.3-26.0)	88.9 (68.3-100.0)	16.7 (0.0-46.5)	8.1 (0.0-16.9)	0.0 (0.0-0.0)
Older (n = 724)	27.4 (24.1-30.6)	78.9 (70.5-87.3)	48.2 (29.3-67.0)	22.8 (18.8-26.8)	2.4 (0.0-5.7)
Period 2					
Overall survival					
Total (n = 2,801)	60.7 (58.9-62.5)	93.9 (91.7-96.2)	77.2 (72.0-82.4)	57.5 (54.9-60.1)	12.2 (8.0-16.3)
Younger (n = 178)	56.7 (49.5-64.0)	100.0 (100.0-100.0)	66.7 (46.5-86.8)	45.7 (34.0-57.4)	16.7 (3.3-30.0)
Older (n = 2,623)	60.9 (59.1-62.8)	93.4 (90.9-95.8)	78.2 (72.8-83.5)	58.2 (55.5-60.8)	11.5 (7.2-15.9)
Progression-free survival					
Total (n = 2,561)	47.3 (45.4-49.2)	87.8 (84.5-91.0)	67.9 (62.0-73.7)	45.4 (42.7-48.0)	9.8 (6.1-13.4)
Younger (n = 176)	46.0 (38.7-53.4)	94.3 (86.6-100.0)	52.2 (31.7-72.6)	37.3 (26.4-48.3)	16.1 (3.2-29.1)
Older (n = 2,385)	47.4 (45.4-49.4)	87.1 (83.6-90.6)	69.5 (63.5-75.5)	45.9 (43.1-48.6)	8.9 (5.2-12.6)
Period 3					
Overall survival					
Total (n = 5,211)	63.8 (62.5-65.1)	96.6 (95.5-97.7)	83.3 (80.8-85.7)	58.3 (56.2-60.5)	9.4 (6.9-11.9)
Younger (n = 331)	52.9 (47.5-58.2)	98.6 (95.7-100.0)	80.0 (66.8-93.2)	49.2 (40.2-58.1)	6.7 (0.4-13.0)
Older (n = 4,880)	64.6 (63.2-65.9)	96.4 (95.3-97.6)	83.4 (80.9-85.8)	58.9 (56.7-61.1)	9.8 (7.0-12.5)
Progression-free survival					
Total (n = 4,635)	50.1 (48.6-51.5)	91.3 (89.4-93.2)	74.4 (71.4-77.5)	43.7 (41.4-45.9)	4.3 (2.6-6.0)
Younger (n = 318)	39.6 (34.2-45.0)	96.4 (91.6-100.0)	71.9 (56.3-87.5)	31.7 (23.5-39.9)	5.9 (0.3-11.5)
Older (n = 4,317)	50.9 (49.4-52.3)	90.9 (88.9-92.9)	74.5 (71.5-77.6)	44.5 (42.2-46.9)	4.1 (2.4-5.9)
Period 4					
Overall survival					

Total (n = 5,010)	86.3 (85.2-87.3)	98.7 (98.0-99.4)	94.1 (92.3-95.9)	83.5 (81.5-85.5)	53.0 (47.0-59.0)
Younger (n = 292)	86.0 (81.7-90.4)	100.0 (100.0-100.0)	96.9 (90.8-100.0)	83.6 (75.8-91.4)	55.5 (37.5-73.5)
Older (n = 4,718)	86.3 (85.2-87.4)	98.6 (97.9-99.3)	94.0 (92.1-95.8)	83.5 (81.4-85.6)	52.8 (46.5-59.1)
Progression-free survival					
Total (n = 4,738)	69.8 (67.9-71.7)	92.2 (89.4-94.9)	84.8 (81.9-87.7)	66.5 (63.3-69.6)	6.8 (0.3-13.4)
Younger (n = 292)	65.5 (58.4-72.6)	95.3 (88.6-100.0)	80.3 (60.7-99.9)	62.0 (50.9-73.1)	0.0 (0.0-0.0)
Older (n = 4,446)	70.1 (68.1-72.0)	91.9 (89.0-94.9)	85.0 (82.1-87.9)	66.8 (63.5-70.0)	7.7 (0.4-15.1)

Figure 3 revealed the Kaplan-Meier curves for OS between the younger and older groups (Fig. 3). The analysis showed younger patients had a worse survival outcome in stage III ($P = 0.0095$) but a better prognosis in stage I ($P = 0.03$). However, no significant difference was found in stage II and stage IV ($P = 0.60$, $P = 0.37$, resp.).

Prognostic Factors in Univariate and Multivariate Analyses

To investigate the significant factors impacting survival outcomes in young patients with GC, univariate and multivariate analyses were performed. The results revealed significantly different survival of GC based on the following parameters (Table 3): the period of diagnosis, drinking consumption, overweight/obesity ($BMI \geq 23$, < 27.4), Weight loss $\geq 10\%$, H. pylori infection, distal tumor location, Borrmann IV, Linitis plastica, poor differentiation, pTNM stage II, III, and IV, Vascular invasion, and surgical margin (all $P < 0.05$). For the younger adults, prognosis factors only involved diagnosis period 4 ($P < 0.0001$), distal tumor location ($P = 0.0007$), Linitis plastica ($P = 0.024$), pTNM stage III ($P < 0.0001$), pTNM stage IV ($P < 0.0001$), and surgical margin ($P = 0.011$) (Supplementary Table 1).

Table 3

Univariate and multivariate survival analysis of predictors associated with overall survival for gastric cancer (bidirectional cohort 1998–2018).

Prognostic Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P Value	Hazard ratio	95% CI	P Value
Period of diagnosis						
Period 1 (1998–2003)	1.00			1.00		
Period 2 (2004–2008)	0.54	0.48–0.61	< 0.0001	0.55	0.49–0.62	< 0.0001
Period 3 (2009–2013)	0.42	0.42–0.53	< 0.0001	0.60	0.53–0.69	< 0.0001
Period 4 (2014–2018)	0.18	0.16–0.21	< 0.0001	0.24	0.20–0.28	< 0.0001
Gender						
Male	1.00					
Female	1.06	0.99–1.14	0.091			
Smoking history						
No	1.00					
Yes	0.90	0.84–0.96	0.0009			
Unknown	1.06	0.89–1.25	0.54			
Drinking history						
No	1.00			1.00		
Yes	0.88	0.82–0.94	0.0001	0.93	0.87–1.00	0.045
Unknown	1.06	0.89–1.25	0.52	0.86	0.70–1.07	0.18
BMI (kg/m²) at diagnosis						
< 18.5	1.17	1.04–1.32	0.0080	1.05	0.93–1.19	0.42
18.5–22.9	1.00			1.00		
23–27.4	0.80	0.74–0.85	< 0.0001	0.93	0.86–1.00	0.036
≥ 27.5	0.75	0.68–0.83	< 0.0001	0.94	0.85–1.05	0.25
Unknown	1.51	1.31–1.74	< 0.0001	1.14	0.96–1.35	0.14
Weight loss						
None	1.00			1.00		
< 10%	1.38	1.28–1.48	< 0.0001	1.05	0.97–1.13	0.22
≥ 10%	2.14	1.95–2.35	< 0.0001	1.22	1.11–1.35	< 0.0001
Unknown	1.82	1.67–1.99	< 0.0001	1.07	0.97–1.19	0.16
H. pylori infection						
Negative	1.00			1.00		
Positive	1.64	1.32–2.05	< 0.0001	1.29	1.03–1.61	0.024
Unknown	3.09	2.62–3.66	< 0.0001	1.54	1.30–1.83	< 0.0001
Primary tumor location						
Proximal	1.00			1.00		
Distal	0.87	0.81–0.92	< 0.0001	0.93	0.87–1.00	0.038
Overlapping lesions	1.56	1.36–1.78	< 0.0001	1.10	0.96–1.27	0.18
Unknown	1.20	1.02–1.40	0.026	0.65	0.53–0.80	< 0.0001
Lauren classification						
Intestinal	1.00			1.00		
Diffuse	1.83	1.58–2.12	< 0.0001	1.17	0.99–1.38	0.069
Mixed	1.36	1.14–1.61	0.0005	0.97	0.81–1.15	0.70

Prognostic Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P Value	Hazard ratio	95% CI	P Value
Unknown	3.75	3.33–4.23	< 0.0001	1.09	0.93–1.27	0.30
Bormann classification						
Bormann I	1.00			1.00		
Bormann II	0.94	0.83–1.07	0.37	0.90	0.79–1.02	0.089
Bormann III	1.17	1.03–1.33	0.019	0.97	0.85–1.11	0.68
Bormann IV	2.48	2.13–2.88	< 0.0001	1.40	1.19–1.65	< 0.0001
Mixed	0.42	0.25–0.70	0.0009	0.97	0.57–1.63	0.90
Unknown	2.50	2.21–2.84	< 0.0001	1.06	0.93–1.21	0.42
Linitis plastica						
No	1.00			1.00		
Yes	2.33	1.84–2.94	< 0.0001	1.29	1.01–1.64	0.044
Unknown	1.51	1.33–1.71	< 0.0001	0.85	0.72–0.99	0.042
Differentiation						
Well	1.00			1.00		
Moderate	3.10	2.03–4.74	< 0.0001	1.45	0.94–2.22	0.090
Poor	4.48	2.94–6.83	< 0.0001	1.56	1.02–2.40	0.041
Undifferentiated	0.001	0.001–999.999	0.91	0.000	0.000–999.999	0.90
Unknown	9.73	6.39–14.81	< 0.0001	1.59	1.02–2.48	0.042
HER2 score						
0 (-)	1.00			1.00		
1 (+)	0.84	0.74–0.96	0.0082	0.96	0.85–1.09	0.54
2 (++)	0.71	0.59–0.84	0.0001	0.90	0.75–1.08	0.27
3 (+++)	1.05	0.85–1.29	0.68	1.08	0.87–1.33	0.51
Unknown	2.41	2.20–2.64	< 0.0001	1.21	1.06–1.37	0.0042
Pathologic T-stage						
T0 + Tis	2.67	1.17–6.08	0.020	1.38	0.19–10.14	0.75
T1	1.00			1.00		
T2	2.72	2.10–3.51	< 0.0001	1.44	1.07–1.95	0.017
T3	7.01	5.70–8.62	< 0.0001	2.10	1.51–2.92	< 0.0001
T4	11.29	9.24–13.80	< 0.0001	2.55	1.82–3.57	< 0.0001
TX	19.07	15.58–23.33	< 0.0001	2.50	1.72–3.62	< 0.0001
Pathologic N-stage						
N0	1.00			1.00		
N1	2.28	1.98–2.63	< 0.0001	1.27	1.09–1.49	0.0020
N2	3.52	3.09–4.00	< 0.0001	1.74	1.48–2.04	< 0.0001
N3	6.85	6.11–7.67	< 0.0001	2.82	2.41–3.29	< 0.0001
NX	8.72	7.79–9.75	< 0.0001	1.74	1.35–2.26	< 0.0001
Pathologic M-stage						
M0	1.00					
M1	5.76	5.34–6.22	< 0.0001			
MX	1.98	1.78–2.20	< 0.0001			
pTNM stage						

Prognostic Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P Value	Hazard ratio	95% CI	P Value
0	2.53	1.04–6.19	0.042	1.76	0.20–15.49	0.61
I	1.00			1.00		
II	3.70	2.99–4.57	< 0.0001	1.69	1.23–2.32	0.0012
III	10.42	8.66–12.54	< 0.0001	1.85	1.29–2.66	0.0009
IV	39.04	32.23–47.29	< 0.0001	5.04	3.42–7.42	< 0.0001
Unknown	13.19	10.88–15.99	< 0.0001	1.80	1.21–2.68	0.0036
Lymphatic invasion						
No	1.00					
Yes	1.76	1.62–1.92	< 0.0001			
Unknown	3.73	3.47–4.00	< 0.0001			
Vascular invasion						
No	1.00			1.00		
Yes	1.77	1.63–1.92	< 0.0001	1.17	1.07–1.28	0.0006
Unknown	3.74	3.48–4.01	< 0.0001	1.17	1.00–1.38	0.054
Nerve invasion						
No	1.00					
Yes	1.06	0.96–1.16	0.23			
Unknown	3.15	2.95–3.37	< 0.0001			
Therapeutic regimen						
Surgery only	1.00			1.00		
Multimodality treatment	3.73	3.04–4.58	< 0.0001	1.09	0.88–1.34	0.44
Unknown	5.67	4.64–6.93	< 0.0001	1.28	1.04–1.57	0.022
Surgical margin						
Negative	1.00			1.00		
Positive	2.47	2.08–2.94	< 0.0001	1.24	1.04–1.48	0.015
Unknown	3.10	2.91–3.30	< 0.0001	1.28	1.10–1.50	0.0020
Age group						
Younger group (< 40 years)	1.00			1.00		
Older group (≥ 40 years)	0.80	0.71–0.90	0.0001	0.92	0.82–1.04	0.20
The final model was built by using stepwise selection with minimized AIC, and the covariates included in the final models were selected by the stepwise selection method, with a significant level for adding variables of 0.05 and a significant level of removing variables of 0.10.						

In the univariate analysis, older patients with GC had better survival outcomes than the younger (HR = 0.80, 95% CI: 0.71–0.90, P = 0.0001). After stratification by pTNM stage, compared to the older, younger group showed a better prognosis in stage I (P = 0.04) but worse in stage III (P < 0.01) (Supplementary Table 2). However, the multivariate analysis demonstrated that younger age was not an independent factor for poor survival outcomes (P = 0.20). In subdivided pTNM stages, a comparison presented that younger group was associated with worse survival outcomes in tumor stage III (P = 0.014), but no statistical significance in stages I, II, and IV (P = 0.074, 0.59 and 0.76, resp.).

Genetic alterations of younger patients with GC

The genetic alterations of GC patients from the China National Cancer Center were shown in Fig. 4A and Supplementary Fig. 1. Of 29 eligible patients with cancer genomics data, 20 were older (68.9%), and the rest of 9 were younger (31.1%). Although no statistical disparity was found in the mutational profile, younger patients have a higher mutation frequency in *RHOA* (33% versus 15%), *CDH1* (22% versus 5%), *KMT2D* (22% versus 10%), *SMAD4* (11% versus 0%), *ARID1A* (11% versus 5%), *ATM* (11% versus 5%), *CTNNB1* (11% versus 5%), and *PIK3CA* (11% versus 5%), while older patients had dominated in *TP53* (70% versus 44%), *LRP1B* (30% versus 11%), *FGFR2* (20% versus 0%), *ARID2* (15% versus 0%), *EP300* (15% versus 0%), *GNAS* (15% versus 11%), *IRS2* (15% versus 11%), *BRCA2* (10% versus 0%), and *APC* (5% versus 0%). Moreover, a high-volume analysis of the relationship between genetic alterations and age groups was

further performed via the TCGA and MSKCC databases (Fig. 4B and Supplementary Fig. 2). GC tissues from older patients had higher likelihoods of *LRP1B* (30% versus 9%, $P < 0.05$), *KMT2D* (13% versus 0%, $P < 0.05$), *APC* (13% versus 2%, $P < 0.05$), *GNAS* mutations (11% versus 1%, $P < 0.05$) than the younger. Similar to the China National Cancer Center, although no significant differences were found, younger patients had mutation predominance in *CDH1* (17% versus 9%), *RHOA* (7% versus 5%), and *CTNNB1* mutations (9% versus 6%). In addition, of the pooled 8 gastric adenocarcinoma datasets, high-TMB was closely associated with older age at diagnosis ($P < 0.0001$) (Supplementary Fig. 3).

Discussion

Our study provided a comprehensive analysis of younger GC patients at clinical and molecular levels. A primary finding was the stable proportion and significant survival improvements of younger cases in the China National Cancer Center from 1988 to 2018. Younger age was proven to be an independent prognostic factor for GC patients in pTNM stage III, while patients in stage I, stage II, and stage IV had similar survival among different age groups. Compare to the younger, a higher mutation frequency of *LRP1B*, *KMT2D*, *APC*, and *GNAS* genes in older patients was demonstrated in the current sequencing analysis, which might partly explain the histopathological behaviors and prognosis between the young and old groups.

Consistent with the previous study [10–15, 23, 24], our findings revealed unique clinical features in younger patients, including female dominance, higher proportions of poor differentiation, and advanced tumor stage. Although the mechanisms for female predominance in younger patients were not clear, some studies indicated that hormonal factors might account for the sex difference [25, 26]. Apart from *H. pylori* infection [27] and some gene distinctions [28], the vague symptoms and delayed diagnosis were also considerable reasons for the advanced stage of younger patients [29, 30].

With an increase of 41.6% for the younger group and 45.9% for the older group, a significant 5-year survival improvement of GC was revealed in our center, which was in line with the increasing trend of pTNM stages I and II, surgery, and multimodality treatment. In China, survival trends of GC could be attributed to an improvement of quality of clinical services, including the improved access to primary healthcare, greater availability of diagnostic facilities, as well as enhanced effectiveness of the treatment [4]. Until 2015, the screening and early detection programs including GC have expanded to 31 provinces [31]. Encouragingly, the detection rate of GC has increased steadily benefit from the large-scale application of upper gastrointestinal endoscopy [32]. In addition, the widespread decision-making by the multi-disciplinary team (MDT) [33] and the emergence of individually multimodal therapies [34] were also closely related to a better prognosis for GC.

To date, survival outcomes of younger patients were still controversial. Previous studies suggested younger patients had a worse survival [14, 15], while several analyses showed on difference [12, 13]. Current data demonstrated a worse prognosis for younger patients in pTNM stage III, whereas other stages showed similar survival. Therefore, variations of prognosis between the younger and older group might be related to stage distributions. Compare to older patients, the higher proportion of multimodality treatment in younger reflected a better tolerance for GC, while more advanced stage and aggressive behaviors might be related to a worse survival in this subpopulation [14]. Besides, the reduced organ functions and rising risk of comorbidities also potentially effect GC prognosis that occurred with age [35]. In addition, although genomic profiles of younger patients were not yet fully ascertained, several studies demonstrated a strong association between certain gene mutations and the prognosis of GC among age groups [16, 17].

The present study observed the differences in the prevalence of several gene mutations between younger and older patients, indicating a specific mutational spectrum in younger patients with GC. Significantly, a higher prevalence of *LRP1B* mutations were identified in old patients. *LRP1B* encoded a unique low-density lipoprotein receptor (LDLR) that functioned in the binding and internalization of ligands [36]. Until now, the concrete functions of *LRP1B* in carcinogenesis were controversial [37–40]. Considered as a tumor suppressor, several findings indicated the impaired *LRP1B* expression could promote the proliferation, migration, and invasion of carcinoma cells [38, 39]. However, the latest update of the Network of Cancer Genes (NCG 6.0) listed *LRP1B* as a potentially false-positive tumor suppressor [39]. Zhou et al. [40] also demonstrated *LRP1B* was one of the recurrently mutated driver genes, which was strongly associated with the development of GC. Further analysis was required to investigate the pathobiological property of *LRP1B* in GC.

We also observed that older patients had a higher likelihood of *GNAS* mutations than younger. *GNAS* was situated on chromosome 20q13.3 and encoded alpha subunit of the stimulatory G-protein [41]. It was suggested that mutations of *GNAS* caused the activation of Wnt and ERK1/2 MAPK pathways via autonomous synthesis of cyclic adenosine monophosphate (cAMP), thus promoting intestinal tumorigenesis [42]. After that, several studies demonstrated the frequent *GNAS* mutations in gastric adenocarcinoma [43, 44]. Consistent to current study, Esser et al. [41] also indicated the expression of *GNAS* was more prevalent in well- and moderately-differentiated GC, which was potentially correlated with older patients. Although the underlying mechanism was currently unclear, *GNAS* mutation might potentially affect the progression of GC via the protein kinase A (PKA), MAPK, and Wnt signaling pathways [45].

As in the past reports [46, 47], our analysis showed older patients had a higher prevalence of *APC* mutation than younger. Long considered a canonical tumor suppressor, *APC* could inhibit the excessive proliferation of tumor cells via regulating Wnt signaling pathway [48]. Mutation of *APC* was common in GC, particularly in well-differentiated adenocarcinoma [49, 50]. Zhan et al. [51] proposed a strong synergy between *APC* alterations and *MEK* inhibitors in enhancing the signaling output of the Wnt cascades. Gerner et al. [52] also observed mutant *APC* was associated with the elevation of nitric oxide synthase 2 and the dysregulation of polyamine metabolism. These data suggested that *APC* mutation might contribute to the oncogenesis of GC. In addition, a recent study also demonstrated a significant association target high expression of *APC* and adverse prognosis of GC patients [53]. The observed prognostic alteration could be the result of the disruption of Wnt cascades, metabolic dysregulation, or some other unknown mechanisms.

KMT2D was among the most frequently mutated genes in some types of cancer including GC [54–57]. Through encoding histone methyltransferase, *KMT2D* was critically involved in the epigenetic and transcriptional regulation of certain tumor-associated genes [56–60]. Lv et al. [56] suggested that *KMT2D* potentially prompt prostate carcinogenesis and metastasis via activating *LIFR* and *KLF4* gene. Later, Xiong et al. [57] confirmed that *KMT2D* might play a role in cell proliferation and apoptosis of GC via the down-regulation of *PTEN* and up-regulation of *LIFR* and *KLF4*. However, recent studies also found the inhibiting effects of *KMT2D* in medulloblastoma [58], lung tumors [59], and lymphoma [60], as *KMT2D* could activate some specific pro-apoptotic genes or

repress certain genes related to cell growth and survival pathways. The above results revealed that the *KMT2D* gene had different functions and biological effects depending on the type of cancer. Furthermore, several studies indicated that mutations of *KMT2D* were substantially higher in older patients than in younger [61, 62], and the age disparity was also demonstrated in our analysis. More experimental studies were necessary to elucidate the underlying functions of *KMT2D* in GC among age groups.

Our study has several strengths. First, clinicopathological characteristics and survival trends of the younger patients from 1998 to 2018 were comprehensively described based on NCCGCDB, which might serve as a reference for a large population-based study in China. Second, our study, for the first time, suggested distinctive mutation disparities including *LRP1B*, *GNAS*, *APC*, and *KMT2D* genes in younger and older patients, which might partly explain the progression and survival of GC among age groups in molecular levels. The major limitation of our study was the insufficient sequencing sample size, particularly for pTNM subtype analysis. As such, possibility might not be ruled out for some of the significant findings. Based on the TCGA and MSKCC, we further analyze a larger-volume sequencing sample to compare genetic alterations among age groups. In addition, regional and racial disparity of younger patients from China and western countries might also exist, which could affect the clinicopathological and molecular property of GC potentially. Therefore, parts of findings from TCGA and MSKCC might not be strongly generalizable to Chinese patients. Finally, some variables including tumor markers, neoadjuvant therapy, and adjuvant therapy were also needed to compare between the younger and older patients.

Conclusions

Our study found a stable proportion of young cases and significant survival improvements of younger patients in the China National Cancer Center from 1998 to 2018. Multivariate analysis suggested that younger patients with pTNM stage III had a worse survival than older, while other tumor stages showed no difference. Distinctive genetic alterations were further identified in younger patients, thus improving precision and personalized medicine in this subpopulation. Further large-scale studies are warranted to investigate more molecular characteristics and related mechanisms for GC patients at younger age.

Abbreviations

GC: gastric cancer; NCCGCDB: China National Cancer Center Gastric Cancer Database; OS: overall survival; AJCC: the American Joint Committee on Cancer; PFS: progression-free survival; NGS: next-generation sequencing; SNVs: single nucleotide variants; INDELs: insertion-deletions; TMB: tumor mutational burden; HR: hazard ratio; LDLR: low-density lipoprotein receptor; cAMP: cyclic adenosine monophosphate; PKA: the protein kinase A

Declarations

Ethics approval and consent to participate

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. This study was approved by the ethics committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 17-156/1412).

Consent for publication

Informed consent was obtained from all participants for publication.

Availability of data and materials

All data generated during this study are included in this published article and its supplementary files.

Competing interests

No potential conflicts of interest were disclosed.

Funding

This work was supported in part by the National Key R&D Program of China (No. 2017YFC0908300).

Authors' contributions

YC and DZ considered and designed the study. PN, HH and LZ performed experiments. TW, XZ and WW did data analyses. TW, XZ and WW collected tumor samples, tissue specimens and clinical data. PN, HH and LZ wrote the manuscript. YZ and CG contributed to the revision of manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank anonymous reviewers and editor for reading and commenting on the manuscript.

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Figures

Figure 1

Changing trends of the proportion of younger and older groups by period and pTNM tumor stage.

Figure 2

Survival trends between younger and older groups during 20 years. A: The 5-year overall survival. B: The 5-year progression-free survival

Figure 3

Kaplan-Meier survival curves of gastric cancer patients between YG and OG. A: Kaplan-Meier survival curves of patients in pTNM stage I. B: Kaplan-Meier survival curves of patients in pTNM stage II. C: Kaplan-Meier survival curves of patients in pTNM stage III. D: Kaplan-Meier survival curves of patients in pTNM stage IV.

Figure 4

Comparison of mutation frequencies between younger and older groups. A: Genetic alterations from the China National Cancer Center. B: Genetic alterations from the TCGA and MSKCC databases.

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