Therapeutic options and clinical outcomes of 1261 patients with mantle cell lymphoma in China — a real-world retrospective multicenter analysis from Chinese Hematologist and Oncologist Innovation Cooperation of the excellent (CHOICE)

Qingqing Cai (caiqq@sysucc.org.cn)
Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center

Dongfeng Zeng
Department of Hematology, Daping Hospital, Army Medical University (Third Military Medical University)

Yu Fang
Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center

Yue Fei
Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Resea

Rong Liang
Department of Hematology, Department of Internal Medicine, Xijing Hospital, Air Force Militery Medical University

Haige Ye
Department of Hematology, The First Affiliated Hospital of Wenzhou Medical UniversityWenzhou Medical University

Yun Liang
Department of Hematologythe Second Affiliated Hospital, Zhejiang University School of Medicine

Xiuhua Sun
Second Affiliated Hospital of Dalian Medical University

Michael Wang
The University of Texas MD Anderson Cancer Center

Huiqiang Huang
Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center

Lugui Qiu

State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Ac

Tiejun Gong

Institute of Hematology and Oncology, Harbin First Hospital

Donglu Zhao

Institute of Hematology and Oncology, Harbin First Hospital

Yuxuan Che

Second Affiliated Hospital of Dalian Medical University

Jinni Wang

Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center

Panpan Liu

Department of Medical Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center

Yi Wang

State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Ac

Tao Pan

Department of Lymphoma & Hematology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University

Yao Lv

Department of Hematology, Department of Internal Medicine, Xijing Hospital, Air Force Militery Medical University

Panruo Jiang

Department of Hematology, The First Affiliated Hospital of Wenzhou Medical UniversityWenzhou Medical University

Xuzhao Zhang

Department of Hematologythe Second Affiliated Hospital, Zhejiang University School of Medicine

Jintai Deng

Second Affiliated Hospital of Dalian Medical University

Shuhua Yi

State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Ac

Yizi He

Department of Lymphoma & Hematology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University

Ling Xiao
Department of Histology and Embryology of School of Basic Medical Science, Central South University
Huijuan Lv
Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Resea
Jiangfang Feng
Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Resea
Huan Xie
Department of Hematology, Daping Hospital, Army Medical University (Third Military Medical University)
Jiacheng Qian
Department of Hematology, Department of Internal Medicine, Xijing Hospital, Air Force Militery Medical University
Huilai Zhang
Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Resea
Hui Zhou
Department of Lymphoma & Hematology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University

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Research Article

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Abstract

Background: Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin B-cell lymphoma and therapeutic options of MCL are limited. We conducted a real-world, multicenter study enrolled 1261 MCL patients from nine medical centers in China to evaluate patients' outcomes.

Methods: This retrospective study enrolled 1261 adult MCL patients between January 2000 and December 2020 from nine medical centers in China. Patients' characteristics, treatment and survival outcomes were evaluated.

Results:145 patients (11%) received Bruton's tyrosine kinase inhibitors (BTKi)-containing regimens as frontline therapy. 12% of the younger patients received autologous hematopoietic stem cell transplantation (AHCT) consolidation. The estimated 2-year progression-free survival (PFS) and 5-year overall survival (OS) rate from the initiation of front-line treatment for the entire cohort was 62.4% and 57.2% respectively. Age≥65 years, high-risk Mantle Cell Lymphoma International Prognostic Index (MIPI), Ki-67>30% and blastoid/pleomorphic histology were associated with shorter PFS or OS. For younger patients, induction therapy with BTKi-containing regimens yield similar efficacy in 3-year PFS and OS as compared to the standard high-dose immunochemotherapy with AHCT (65.5% vs 66.6%, p=0.907 and 84.8% vs 92.3%, p=0.204). For the relapsed or refractory MCL patients in this cohort, the 5-year OS from the initiation of salvage therapy was 36.0%. A total of 23 patients developed hepatitis B virus (HBV) reactivation after immunochemotherapy, while BTKi treatment was not associated with higher rate of HBV reactivation.

Conclusions: In conclusion, for younger Chinese MCL patients, the addition of BTKi in frontline therapy is a safer and more convenient alternative treatment strategy. For MCL patients with resolved hepatitis B, anti-HBV prophylaxis should not be neglected.

Introduction

Mantle cell lymphoma (MCL) is a rare and aggressive subset of B-cell lymphomas, accounting for 3% of all mature non-Hodgkin's lymphomas in the United States and 5–7% of all malignant lymphomas in Western Europe (1, 2). MCL is characterized by heterogenous clinical courses ranging from highly aggressive cases with poor prognosis to disseminated indolent cases that do not require treatment for years(2, 3). The epidemiology and outcomes of MCL patients have been well documented in Western countries, however, this information is largely lacking in patient populations from China. MCL accounts for 2.6 to 5% of total non-Hodgkin lymphoma cases in different regions within China(4–8). The reported 5-year overall survival (OS) and progression-free survival (PFS) rates in China in 2017 were 35.5% and 8.8%(9), according to a single-center study including only 66 MCL patients. This small sample size makes it difficult to reflect the actual survival outcome of Chinese MCL population.

Great advances have been made in recent years in the treatment of MCL, with acknowledgement of the benefit of induction immunochemotherapy containing high-dose cytarabine and autologous

hematopoietic cell transplantation (AHCT) in younger patients(10–14). The introduction of less intensive regimens such as BR (bendamustine and rituximab) and VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone) have offered more appropriate therapeutic options for older and unfit patients(15, 16). Maintenance rituximab has also significantly prolonged overall survival after AHCT and after induction therapy in patients who are not eligible for AHCT(17, 18). Notably, Bruton's tyrosine kinase inhibitors (BTKi) showing the most remarkable response rate and improving the outcome of patients with relapsed or refractory disease(19–21).

Currently, updated international guidelines are being followed in the treatment of MCL in China, but the treatment options are also restricted by drug availability and reimbursement status. In particular, Chinese patients may have specific comorbidities, such as hepatitis B virus (HBV) infection, which could be reactivated by rituximab-containing chemotherapy. Therefore, the treatment pattern of MCL in China may be different and it is unclear whether guidelines from Western regions are appropriate for Chinese population. Here, we performed a retrospective multicenter study and summarized the clinical features, treatment patterns and survival outcomes of the Chinese MCL population, aiming to promote the appropriate MCL management in China.

Method

Patients and data collection

We retrospectively collected data of patients diagnosed with MCL between January 2000 and December 2020 at 9 medical centers in China. The diagnosis of MCL was made by hematopathologists at each institution. Data were collected for each patient including baseline characteristics, treatment, and outcomes. The simplified MCL international prognostic index (MIPI) score was calculated for each patient with sufficient data as previously published(22). Response to induction treatment was defined by each participating center using institutional standard imaging modalities at the time of treatment. The project was approved by the institutional review board of each participating center.

Statistical analysis

The primary objective was to characterize first-line treatment patterns and survival outcomes of the Chinese MCL population. Baseline characteristics and therapies were compared among groups using chi-square and Fisher's exact tests as appropriate. Survival curves were calculated using the Kaplan–Meier method. Cox proportional hazards models were used to determine the impact of demographic and clinical variables on survival outcomes. Variables examined for impact on survival included age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), stage, MIPI score, blastoid/pleomorphic histology, Ki-67, bone marrow involvement, hepatitis B virus infection and treatment. Significant variables based on univariate analyses were included in multivariate analyses (MVA). To minimize selection bias from baseline characteristics among certain groups described below, propensity score matching (PSM) was performed using nearest neighbor 1:1 matching method with caliper width of 0.2. P value < 0.05 was considered statistically significant.

Result

Patients’ characteristics and treatment patterns of the entire cohort

Data from a total of 1372 patients were collected and those missing substantial data on stage, treatment, or outcome were excluded (n = 111). A total of 1261 patients were included in the final analysis. Patient and treatment characteristics are listed in Table 1. The median age at diagnosis was 59 years, with 912 patients < 65 years. 326 (26%) and 243 (10%) of 1178 patients with available MIPI had intermediate and high risk, respectively. 117 patients (9%) had blastoid/pleomorphic MCL. 396 patients (31%) had bone marrow involvement.

Table 1
Demographic, clinical and first-line treatment data for MCL patients.

Characteristic	No. (%)			*P*
	All patients (n = 1261)	Age < 65 (n = 912)	Age ≥ 65 (n = 349)	
Sex				
Male	973 (77)	706 (77)	267 (77)	0.764
Female	288 (23)	206 (23)	82 (23)	
ECOG PS				
0–1	1054 (84)	786 (86)	268 (77)	< 0.001
≥ 2	151 (12)	83 (9)	68 (19)	
Missing	56 (4)	43 (5)	13 (4)	
Ann Arbor Stage				
I or II	147 (12)	108 (12)	39 (11)	0.770
III or IV	1114 (88)	804 (88)	310 (89)	
Simplified MIPI				
Low risk	609 (48)	517 (57)	92 (27)	< 0.001
Intermediate risk	326 (26)	206 (23)	120 (34)	
High risk	243 (19)	120 (13)	123 (35)	
Missing	83 (7)	69 (7)	14 (4)	
Blastoid/pleomorphic:				
Yes	117 (9)	78 (9)	39 (11)	0.159
No	1144 (91)	834 (91)	310 (89)	
Ki-67				

Abbreviations: AHCT, autologous hematopoietic cell transplantation; BTKi, Bruton's tyrosine kinase inhibitor; BR, bendamustine and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine and platinum; ECOG PS, Eastern Cooperative Oncology Group performance status; R-hyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MIPI, Mantle Cell Lymphoma International Prognostic Index; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

[a] Chemo-free regimens: single-agent or the combinations of rituximab, BTK inhibitors and lenalidomide.

Characteristic	No. (%)			*P*
	All patients (n = 1261)	Age < 65 (n = 912)	Age ≥ 65 (n = 349)	
≤ 30%	419 (33)	315 (35)	104 (30)	0.106
> 30%	583 (46)	405 (44)	178 (51)	
Missing	259 (21)	192 (21)	67 (19)	
Extranodal site of lymphoma involvement				
Bone marrow	396 (31)	271 (30)	125 (36)	0.042
Central nervous system	3 (1)	2 (1)	1 (1)	1.000
Mediastinum/myocardium	16 (1)	15 (1)	1 (1)	0.086
Lung	31 (2)	16 (2)	15 (4)	0.014
Liver	38 (3)	23 (3)	15 (4)	0.139
Pancreas	9 (1)	5 (1)	4 (1)	0.272
Thyroid	4 (1)	3 (1)	1 (1)	1.000
Spine	2 (1)	2 (1)	0	1.000
Induction regimen				
RCHOP/RDHAP	179 (14)	158 (17)	21 (5)	
R-DHAP	18 (1)	15 (2)	3 (1)	
R-HyperCVAD	55 (4)	51 (5)	4 (2)	
Nordic regimen	25 (2)	23 (2)	2 (1)	
R-CHOP	431 (34)	307 (34)	124 (58)	
BR	37 (3)	11 (1)	26 (7)	
VR-CAP	23 (2)	11 (1)	12 (4)	

Abbreviations: AHCT, autologous hematopoietic cell transplantation; BTKi, Bruton's tyrosine kinase inhibitor; BR, bendamustine and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine and platinum; ECOG PS, Eastern Cooperative Oncology Group performance status; R-hyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MIPI, Mantle Cell Lymphoma International Prognostic Index; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

[a] Chemo-free regimens: single-agent or the combinations of rituximab, BTK inhibitors and lenalidomide.

Characteristic	No. (%)			*P*
	All patients (n = 1261)	Age < 65 (n = 912)	Age ≥ 65 (n = 349)	
Novel agents plus chemotherapy	150 (12)	106 (11)	44	
Chemo-free regimens[a]	43 (4)	19 (2)	24 (7)	
Other	301 (24)	232 (25)	68 (15)	
Anti-CD20 with induction				
Yes	992 (79)	721 (79)	271 (78)	0.591
No	269 (21)	191 (21)	78 (22)	
Cytarabine with induction				
Yes	330 (26)	300 (33)	30 (9)	< 0.001
No	931 (74)	612 (67)	319 (91)	
Novel agent with induction				
BTKi	145 (11)	89 (10)	56 (16)	0.002
Bortezomib	55 (2)	35 (4)	20 (6)	0.165
Lenalidomide	65 (5)	44 (5)	21 (6)	0.395
No	1032 (82)	768 (84)	264 (76)	< 0.001
AHCT in first remission				
Yes	115 (9)	109 (12)	6 (2)	< 0.001
No	1146 (91)	803 (88)	343 (98)	
Post-induction rituximab maintenance				
Yes	214 (17)	173 (19)	41 (12)	0.002
No	1047 (83)	739 (81)	308 (88)	

Abbreviations: AHCT, autologous hematopoietic cell transplantation; BTKi, Bruton's tyrosine kinase inhibitor; BR, bendamustine and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine and platinum; ECOG PS, Eastern Cooperative Oncology Group performance status; R-hyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MIPI, Mantle Cell Lymphoma International Prognostic Index; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

[a] Chemo-free regimens: single-agent or the combinations of rituximab, BTK inhibitors and lenalidomide.

Characteristic	No. (%)			*P*
	All patients (n = 1261)	Age < 65 (n = 912)	Age ≥ 65 (n = 349)	
Was patient enrolled in a therapeutic clinical trial at ANY time?				
Yes	38 (3)	27 (3)	11 (3)	1.000
No	1223 (97)	885 (97)	338 (97)	

Abbreviations: AHCT, autologous hematopoietic cell transplantation; BTKi, Bruton's tyrosine kinase inhibitor; BR, bendamustine and rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine and platinum; ECOG PS, Eastern Cooperative Oncology Group performance status; R-hyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MIPI, Mantle Cell Lymphoma International Prognostic Index; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

[a] Chemo-free regimens: single-agent or the combinations of rituximab, BTK inhibitors and lenalidomide.

Immunochemotherapy was the most common first-line treatment, including R-CHOP in 431 (34%) patients, high-dose cytarabine (HD-AraC) and rituximab-based regimens (R-HD-AraC regimens: R-CHOP/R-DHAP, R-HyperCVAD, R-DHAP, Nordic regimen) in 277 (22%) patients, and BR in 37 (3%) patients. 145 patients (11%) received additional BTKi in first-line therapy. 214 (17%) patients received maintenance rituximab therapy. In the 912 patients < 65 years, 109 patients (12%) patients received autologous hematopoietic cell transplantation (AHCT) consolidation.

Survival outcome and prognostic factors of the entire cohort

The median follow-up was 32.0 months (range: 1-202 month). PFS rates at 2 and 5 years were 62.4% and 40.0% respectively. OS rates at 2 and 5 years were 80.5% and 57.2% respectively. For the patients who had received rituximab-containing regimens as induction therapy (n = 992), PFS rates at 2 and 5 years were 67.6% and 43.7% respectively. In addition, OS rates at 2 and 5 years were 84.4% and 61.6% respectively.

For younger patients with rituximab-containing induction treatment (n = 721), PFS rates at 2 and 5 years were 70.8% and 46.8% respectively. OS rates at 2 and 5 years were 88.6% and 68.9% respectively. For older patients with rituximab-containing induction treatment (n = 271), PFS rates at 2 and 5 years were 58.7% and 35.0% respectively. OS rates at 2 and 5 years were 73.0% and 43.1% respectively.

On unadjusted univariate analysis in the entire cohort, age ≥ 65 years, ECOG PS ≥ 2, high-risk MIPI, blastoid/pleomorphic histology, Ki-67 > 30% and bone marrow involvement were associated with both inferior PFS ($p < 0.001–0.002$) and OS ($p < 0.001–0.003$). Based on the MVA results, age ≥ 65 years, high-risk MIPI and bone marrow involvement were significantly associated with poor OS ($p \leq 0.002–0.012$,

Table 2). Blastoid/ pleomorphic histology, Ki-67 > 30% and high-risk MIPI remained statistically relevant to poor PFS ($p \leq 0.002–0.040$, Table 2).

Table 2
Univariate and multivariable analysis of PFS and OS in the entire cohort

	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
PFS						
Male sex	1.22	0.99–1.51	0.060	-	-	-
Age ≥ 65	1.44	1.10–1.73	< 0.001	1.24	0.98–1.56	0.071
ECOG PS ≥ 2	1.50	1.18–1.90	0.001	1.04	0.75–1.43	0.823
Advanced stage	1.38	1.03–1.84	0.028	1.34	0.96–1.86	0.087
High-risk MIPI	1.92	1.56–2.36	< 0.001	1.38	1.01–1.87	0.040
Blastoid/pleomorphic histology	1.94	1.50–2.51	< 0.001	1.64	1.20–2.25	0.002
Ki-67 > 30%	1.53	1.25–1.88	< 0.001	1.32	1.05–1.66	0.018
BM involvement	1.33	1.11–1.59	0.002	0.91	0.70–1.20	0.512
OS						
Male sex	1.15	0.88–1.49	0.302	-	-	-
Age ≥ 65	1.78	1.43–2.21	< 0.001	1.53	1.16-2.00	0.002
ECOG PS ≥ 2	1.87	1.43–2.44	< 0.001	1.17	0.81–1.69	0.410
Advanced stage	1.34	0.93–1.93	0.113			
High-risk MIPI	2.60	2.06–3.28	< 0.001	1.65	1.16–2.34	0.005
Blastoid/pleomorphic histology	1.65	1.18–2.30	0.003	1.30	0.88–1.93	0.186
Ki-67 > 30%	1.48	1.14–1.91	0.003	1.31	0.99–1.73	0.055
BM involvement	1.72	1.38–2.14	< 0.001	1.48	1.09–2.01	0.012

BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; MIPI, Mantle Cell Lymphoma International Prognostic Index

First-line treatment pattern and survival outcomes of early stage MCL

A total of 147 patients were diagnosed at stage I/II. PFS rates of the stage I/II MCL patients at 2 and 5 years were 69.3% and 53.2% respectively. And OS rates at 2 and 5 years were 83.3% and 63.4% respectively. All patients have received first-line immunochemotherapy and 16 patients (11%) underwent radiotherapy. Progression of disease (POD) within 24 months of diagnosis (POD24) has been identified as a prognostic indicator of poor survival in MCL. POD included primary refractory disease, defined as no response or progression during frontline therapy, and relapsed MCL with the definition of relapse after achieving partial or complete remission at the end of induction therapy(23). The POD24 rate of patients with R-CHOP, R-HD-AraC regimens, chemotherapy plus novel agents, BR, chemo-free regimens and other first-line treatment were 36% (n = 21), 10% (n = 3), 21% (n = 3), 25% (n = 1), 33% (n = 2) and 46% (n = 16), respectively.

First-line treatment pattern and survival outcomes of advanced stage MCL

Younger patients (< 65 years)

A total of 1114 patients were diagnosed at stage III/IV, 804 patients were under 65 years old. PFS rates for this cohort at 2 and 5 years were 64.9% and 40.6% respectively. OS rates at 2 and 5 years were 84.9% and 62.0% respectively. The POD24 rate of younger patients with R-CHOP, R-HD-AraC regimens, chemotherapy plus novel agents, BR and other first-line treatment were 32% (85/264), 27% (58/211), 31% (36/118), 10% (1/10) and 48% (97/201), respectively. We observed no difference in PFS ($p = 0.196$) and OS ($p = 0.871$) in younger MCL patients treated with chemotherapy plus novel agents and R-HD-AraC, while R-CHOP induction was associated with inferior PFS compared with R-HD-AraC ($p = 0.005$; Table S1).

Of the 211 patients receiving R-HD-AraC regimens as first-line therapy, 132 (62%) patients were treated with alternating R-CHOP and R-DHAP (R-CHOP/R-DHAP), 48 (23%) with R-HyperCVAD, 12 (6%) with R-DHAP, and 19 (9%) with Nordic regimen. The POD24 rate of patients with R-CHOP/R-DHAP, R-HyperCVAD, R-DHAP and Nordic regimen were 23% (n = 31), 44% (n = 21), 17% (n = 2) and 21% (n = 4), respectively. PFS and OS were compared among treatment groups (Table S2). In terms of PFS, induction therapy with R-HyperCVAD (vs R-CHOP/R-DHAP, $p = 0.021$) was associated with worse outcome. No significant difference was observed between treatment groups in terms of OS.

118 patients received chemotherapy plus novel agents as first-line therapy. The POD24 rate of patients with BTKi-, lenalidomide- and bortezomib-containing regimens were 29% (19/65), 32% (12/38) and 34% (11/32), respectively. No significant difference was observed among patients treated with three novel agents in terms of PFS ($p = 0.944$) and OS ($p = 0.158$).

153 patients (19%) underwent maintenance rituximab and 104 (13%) underwent consolidated AHCT, including 50 patients also receiving MR. Survival was compared in rituximab-containing induction therapy responders who were treated with AHCT followed by MR (n = 50) versus MR alone (n = 103) versus AHCT alone (n = 48) versus neither (n = 370): 2-year PFS of 94% in AHCT followed by MR group, 72.5% in MR alone group, 58.2% in AHCT alone group and 73.0% in neither ($p = 0.002$; Fig. 1A). and 5-year

OS rates were 86.1% versus 79.0% versus 89.5% versus 63.5% (p = 0.001; Fig. 1B), respectively. AHCT followed by MR significantly improved PFS compared with either MR alone, AHCT alone or neither. In terms of OS, AHCT followed by MR, MR alone and AHCT alone were all associated with better outcome, in comparison with omitting AHCT or MR. For patients achieving CR, PFS improvement persisted for those received AHCT followed by MR (Fig. 1C), but the improvement of OS with these consolidated therapies was diminished (Fig. 1D). We further compared survival outcomes of the patients with or without MR and/or AHCT in patients responding to R-HD-AraC induction therapy and the result was consistent with the entire cohort (Fig. 1E-F). However, benefit in PFS and OS with AHCT and/or MR was not evident in patients responding to chemotherapy combined with novel agents (Fig. 1G-H). Few patients in the R-CHOP group received AHCT (n = 14), preventing meaningful analysis on consolidated modalities in this group.

To evaluate whether the use of BTKi could improve the efficacy and mitigate the toxicity of standard first-line treatment, we compared the outcome of patients receiving R-HD-AraC regimens followed by consolidated AHCT (n = 54) versus non-HD-AraC chemotherapy combined with BTKi without AHCT consolidation (n = 47). Unadjusted univariate analysis demonstrated an improvement in OS favoring use of HD-AraC and AHCT therapy with 3-year OS rate of 90.9% versus 79.1% with BTKi-containing treatment (p = 0.033; Fig. 2B). No significant difference in PFS was observed between two treatment groups, with 3-year PFS of 74.7% with HD-AraC and AHCT therapy versus 54.7% with BTKi-containing treatment (p = 0.114; Fig. 2A). However, selection bias may have influenced the decision for frontline therapy. Therefore, we performed a secondary analysis with propensity score matching and the covariates included age, sex, ECOG PS, stage, MIPI, blastoid/pleomorphic histology, Ki-67 and bone marrow involvement. Twenty-eight patients with each treatment were matched and the baseline characteristics of the matched patients are listed in Table S3. No significant difference in the survival outcomes was observed between two treatment groups, with 3-year PFS of 66.6% with HD-AraC and AHCT therapy versus 65.5% with BTKi-containing treatment (p = 0.907; Fig. 2C), and 3-year OS of 92.3% with HD-AraC and AHCT therapy versus 84.8% with BTKi-containing treatment (p = 0.204; Fig. 2D).

Older patients (≥ 65 years)

Among the patients diagnosed at stage III/IV, 310 patients (27.8%) were ≥ 65 years. PFS rates at 2 and 5 years for this cohort were 52.5% and 31.6% respectively. OS rates at 2 and 5 years were 68.1% and 41.5% respectively. The POD24 rate of older patients with R-CHOP, R-HD-AraC regimens, BR, VR-CAP, BTKi plus chemotherapy, chemo-free regimens and other first-line treatment were 35% (40/114), 48% (14/29), 22% (5/23), 25% (4/16), 46% (12/26), 48% (10/21) and 62% (50/81), respectively. No significant difference was observed in PFS and OS among these treatment groups (Table S4).

Thirty-seven patients (12%) underwent maintenance rituximab and 6 (2%) underwent AHCT consolidation, including one patient also with MR. Survival was compared in patients who were treated with or without MR or AHCT: the 2-year PFS rates were 77.4% versus 51.1% (p = 0.001), and 5-year OS rates were 66.2% versus 40.4% (p = 0.024), respectively. In the secondary analysis excluding patients who

had stable or progressive disease after completion of first-line treatment, MR tended to be associated with improved PFS ($p = 0.052$), but not OS ($p = 0.151$).

Treatment pattern and survival outcomes of relapsed or refractory MCL

A total of 609 patients experienced relapsed or refractory (r/r) disease. The previously mentioned threshold of progression of disease within 24 months since initial diagnosis of MCL was used to define patients as early POD (≤ 24 months; n = 458) or late POD (> 24 months; n = 151) group. The characteristics of patients classified by the timing of POD are listed in Table S5. The 5-year overall survival after initiation of salvage therapy (OS-2) was 36.0%. For the patients with early or late POD, the 5-year OS-2 after initiation of salvage therapy was 32.3% and 47.0%, respectively ($p < 0.001$; Figure S1A).

The salvage treatment data was available in 442 patients were listed in Table S6. 133 patients (30%) have received BTKi alone or as part of any line of salvage treatment. The addition of BTKi into salvage treatment was associated with significantly improved OS-2 (5-year OS-2, 62.0% versus 35.5%, $p < 0.001$; Figure S1B). Additionally, seven patients were managed with chimeric antigen receptor (CAR) T-cell as salvage therapy.

Risk and management of hepatitis B virus (HBV) reactivation

Among 975 patients with available baseline information on HBV infection, no significant difference on PFS and OS was identified between patients with baseline chronic hepatitis B (HBsAg-positive), resolved hepatitis B (HBsAg-negative, anti-HBc-positive) and the remaining patients (Fig. 3A-B). Thirty patients have elevated level of serum HBV DNA at baseline and the survival outcomes of these patients were also similar to those with undetectable or low HBV-DNA level (Fig. 3C-D). 9 (6.3%) patients with positive HBsAg developed HBV reactivation, including 4 patients with anti-HBV prophylaxis. Fourteen (4.8%) patients with negative HBsAg, positive anti-HBc developed HBV reactivation, including 1 patient receiving tenofovir as anti-HBV prophylaxis (Table 3). HBV reactivation was defined according to American Association for the study of liver diseases (AASLD) 2018 Hepatitis B Guidance(24). The cumulative rate of HBV reactivation of patients with BTKi exposure is analogous to those naïve to BTKi treatment, in both HBsAg-positive group ($p = 0.820$) and HBsAg-negative, anti-HBc-positive group ($p = 0.492$; Figure S2). Seven of the 23 patient with HBV reactivation were diagnosed with HBV-related hepatitis.

Table 3
Treatment and outcomes of patients with positive HBsAg or positive anti-HBc.

	HBsAg positive		HBsAg negative, anti-HBc positive	
	Anti-HBV prophylaxis (n = 91)	No anti-HBV prophylaxis (n = 53)	Anti-HBV prophylaxis (n = 43)	No anti-HBV prophylaxis (n = 248)
HBV reactivation	4 (4.4%)	5 (9.4%)	1 (2.3%)	13 (5.3%)
HBV-related hepatitis	1 (1.1%)	3 (5.8%)	0	3 (1.2%)

HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B surface antibody; HBV, hepatitis B virus.

Discussion

To our knowledge, this is the largest retrospective analysis on MCL patients in China. The median age at diagnosis was 59 years, younger than that reported in Western cohorts (68 years)(3). The incidence of bone marrow involvement in this cohort (31%) were much lower than that in Western patients (82%)(25). Other clinical features of MCL patients in our cohort were comparable to those reported in the Western cohorts. The PFS and OS of the patients who have received rituximab-containing induction therapy was analogous to those recently reported in several Western cohorts(26, 27). Younger patient cohort also had similar survival outcomes(25, 28). However, survival outcome of the older patients was significantly inferior compared with that reported in the Western countries(25). Conventional prognostic factors including age ≥ 65 years, high-risk MIPI, blastoid/pleomorphic histology, Ki-67 > 30% and bone marrow involvement were associated with worse PFS or OS on MVA in this cohort.

Most younger and older patients received frontline immunochemotherapy with R-CHOP given the time period of data capture. Unsurprisingly, younger patients with R-HD-AraC regimens as first-line treatment had the lowest rate of POD24, and novel agents-containing regimens also demonstrated favorable outcomes. The most commonly utilized R-HD-AraC regimen was R-CHOP/R-DHAP, and R-HyperCVAD was associated with unsatisfactory disease control, which may be caused by the intolerable toxicity of the R-HyperCVAD regimen. Although previous study has demonstrated a high CR rate with R-HyperCVAD, almost 40% of patients were unable to complete the planned treatment(29). Therefore, R-HyperCVAD is not recommended as induction regimen by the British Society of Hematology (BSH)(30).

For the older patients, first-line regimens used were varied except for R-CHOP in this cohort. Patients who received BR and VR-CAP have achieved the lowest rate of POD24. A recent study has reported that exposure to frontline HD-AraC in older patients appeared to mitigate differences in clinical outcome between younger and older patients(25). In contrast, our study failed to demonstrate the benefit of frontline HD-AraC in older patients. Substantial hematological toxicity of HD-AraC may prevent the

completion of therapy and thus reduction of cytarabine dose is considered as a solution. The combination of a lower dose of cytarabine and BR backbone (RBAC500) has shown a manageable hematological toxicity that allowed 95% of patients to complete at least four RBAC500 cycles with a median age of 71 years, and achieved a 2-year PFS of 81%(31). Overall, less aggressive frontline regimens, especially BR and VR-CAP, are expected to change the adverse outcome of older patients in China. Adjunctive low dose cytarabine and targeted agents could also be considered.

AHCT was uncommon even in patients younger than 65 years in this cohort, suggesting the limited availability and affordability of AHCT in real-world practice in China. Only AHCT followed by MR was associated with better PFS, and AHCT alone was only associated with improved OS in the rituximab-exposed cohort. However, this improvement in OS with AHCT alone did not persist for the CR and novel-agents-exposed cohort. Nevertheless, the value of HD-AraC-based induction therapy followed by consolidated AHCT in the frontline setting is becoming uncertain in the era of targeted therapy. Large retrospective studies in recent years showed that AHCT was not clearly associated with improved OS(27, 28) and the use of novel agents at relapse may help explain the lack of improvement. Also, there is an increasing desire for more convenient and tolerable treatment options that could be widely utilized. Our exploratory analysis demonstrated that the efficacy of BTKi-containing treatment was comparable to that of the standard first-line treatment with R-HD-AraC regimens followed by consolidated AHCT. While the use of PSM has minimized the selection bias, small sample size and heterogeneous chemotherapy regimens that was combined with BTKi may limit the interpretability of the result. Currently, randomized trials are evaluating the necessity of HD-AraC (ECOG 4181 trial; NCT04115631) and consolidated AHCT (TRIANGLE trial; NCT02858258) when BTKi is incorporated in first-line therapy, and results from these trials are expected to change the therapeutic pattern for younger patients. Such effort is also being made by researchers in China, with an ongoing phase II trial (NCT04624958) assessing zanubrutinib induction and maintenance as an alternative of consolidated AHCT.

Similarly, maintenance rituximab was uncommon in our cohort, which may be resulted from limited reimbursement for rituximab as maintenance. Consistent with the phase III Mantle Cell Lymphoma Efficacy of Rituximab Maintenance (LyMA) study and European MCL Elderly Trials(17, 18), our results support the use of maintenance rituximab irrespective of younger or older patients. However, several problems remained in the practice of maintenance rituximab therapy. First, the optimal schedule and duration of rituximab maintenance was difficult to discern for this cohort given the retrospective nature of the study. Maintenance rituximab is typically offered every 2 months and the duration ranges from 2 years to continuous course until disease progression(17, 18). Secondly, rituximab-maintenance therapy was reported to offer survival benefit when used after R-CHOP or R-cytarabine-based therapy in the frontline but the benefit following other induction therapies such as bendamustine- or fludarabine-containing treatment remains unknown(32). Thus, the value of maintenance rituximab following BR and VR-CAP induction is not convincing. Lastly, novel maintenance strategies incorporating other targeted agents are expected as more effective alternatives to maintenance rituximab, especially for older patients. Single-agent lenalidomide maintenance has been shown to improve PFS after R-CHOP + HD-AraC induction and AHCT versus observation, at the cost of an increased rate of adverse events(33).

Currently, the ECOG-ACRIN E1411 trial (NCT01415752) is not only evaluating the use of bortezomib (BR ± bortezomib) in induction therapy, but also comparing maintenance strategies of lenalidomide with rituximab (LR) versus rituximab monotherapy in patients < 65 years. The MCL-R2 Elderly trial (NCT01865110) is also comparing LR versus rituximab maintenance after R-CHOP ± cytarabine induction in patients > 60 years. The SHINE study (NCT01776840) is evaluating ibrutinib-rituximab maintenance after BR ± ibrutinib induction in patients > 65 years.

In this study, patients with consolidated AHCT followed by MR had better PFS compared with MR alone. However, results may have been skewed by the small sample size and inherent limitations of retrospective study; thus, it remains uncertain whether combined AHCT and MR provides advantage over MR alone. The ongoing phase III EA4151 trial (NCT03267433) is comparing these two consolidated modalities in younger patients with negative minimal residual disease in first complete remission.

For the r/r MCL, the OS-2 of our cohort was similar to that reported in the Western cohorts(26, 34). Time to POD confirmed its crucial importance to predict the overall survival. 30% of the r/r MCL received BTK inhibitors during the salvage treatment and demonstrated a good outcome, in accordance with the well-known efficacy of BTKi in relapsed or refractory setting. Since the primary objective of our study was to characterize treatment patterns in the front-line setting, in-depth analysis of salvage treatment pattern in this cohort would remain for further study.

Given the endemic HBV infection, HBV reactivation related to immunosuppressive chemotherapies remains a common but serious complication for Chinese MCL patients. For HBsAg-positive patients, anti-HBV prophylaxis should be initiated at least 7 days before anticancer therapy and drugs with a high resistance barrier (entecavir or tenofovir) are preferred. For HBsAg-negative, anti-HBc–positive patients, anti-HBV prophylaxis is recommended for all the patients receiving rituximab-containing treatment or stem cell transplantation(24, 35). However, preventive measures are not always successfully implemented in these patients, possibly resulted from unawareness of the risk of HBV reactivation and consideration of cost effectiveness of anti-HBV prophylaxis. In the current study, most of the HBsAg-negative, anti-HBc–positive patients did not receive anti-HBV prophylaxis and 5.3% of these untreated patients developed HBV reactivation, including 3 patients with HBV-related hepatitis. This result supported the necessity of anti-HBV prophylaxis in this patient cohort. Except for traditional cytotoxic drugs and anti-CD20 antibody that have been identified as risk factors of HBV reactivation, the association between other targeted agents and HBV reactivation is uncertain. Our preliminary analysis suggested BTKi may not be a risk factor and more solid evidence is needed to decide the prophylaxis recommendation for patients receiving BTKi.

This study has several limitations. First, as a multi-center study, there was a lack of central pathological and response review. Second, as a major consideration of treatment selection, safety profile of the treatment modalities in this patient cohort was not collected and analyzed, thus it is unable to assess whether ethnic characteristics could affect treatment-related side effect. Third, biologic features (i.e., TP53 mutations or deletions) were not included in the analysis because these features were not routinely

tested in clinical practice and may not be available for most of the included patients. Lastly, inherent time bias existed in the analysis of AHCT and maintenance rituximab therapy. To reduce the biases, we conducted secondary analyses that excluded patients with stable or progressive disease during the induction therapy.

Conclusions

In conclusion, for younger patients, adjunctive BTK inhibitors and other targeted agents in the frontline therapy are expected to be an alternative management strategy with more favorable safety and convenience. The outcome of older patients remains poor; thus, more effective and tolerable therapies are urgently needed. For MCL patients with resolved hepatitis B, anti-HBV prophylaxis should not be neglected. Despite the current study with a large cohort, data on the epidemiology and practice pattern of MCL within Chinese population was still limited. Contemporary population-based and hospital-based registries of MCL remains an unmet need in China.

Abbreviations

MCL: Mantle cell lymphoma

BTKi: Bruton's tyrosine kinase inhibitors

AHCT: autologous hematopoietic stem cell transplantation

PFS: progression-free survival

OS: overall survival

MIPI: MCL international prognostic index

HBV: hepatitis B virus

BR: bendamustine and rituximab

VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone

ECOG PS: Eastern Cooperative Oncology Group performance status

MVA: multivariate analyses

PSM: propensity score matching

HD-AraC: high-dose cytarabine

POD: Progression of disease

AASLD: American Association for the study of liver diseases

BSH: British Society of Hematology

RBAC500: The combination of a lower dose of cytarabine and BR backbone

LR: lenalidomide with rituximab

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with Declaration of Helsinki principles. All procedures involving human subjects were approved by the institutional review board of each participating hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

D.Z. and Q.C. designed the study. Y.Fang. did the statistical analysis. Y.Fang., D.Z. and Y.C. wrote the manuscript. Y.Fei., R.L., H.Y., Y.L., X.S., Y.C., M.W., H.H., T.G., D.Z., J.W., P.L., Y.W., T.P., Y.L., P.J., X.Z., J.D, S.Y., Y.H., L.X., H.L., J.F., H.X., J.Q., H. Z., H.Z., D.Z. collected clinical data. All authors read and approved the final manuscript.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

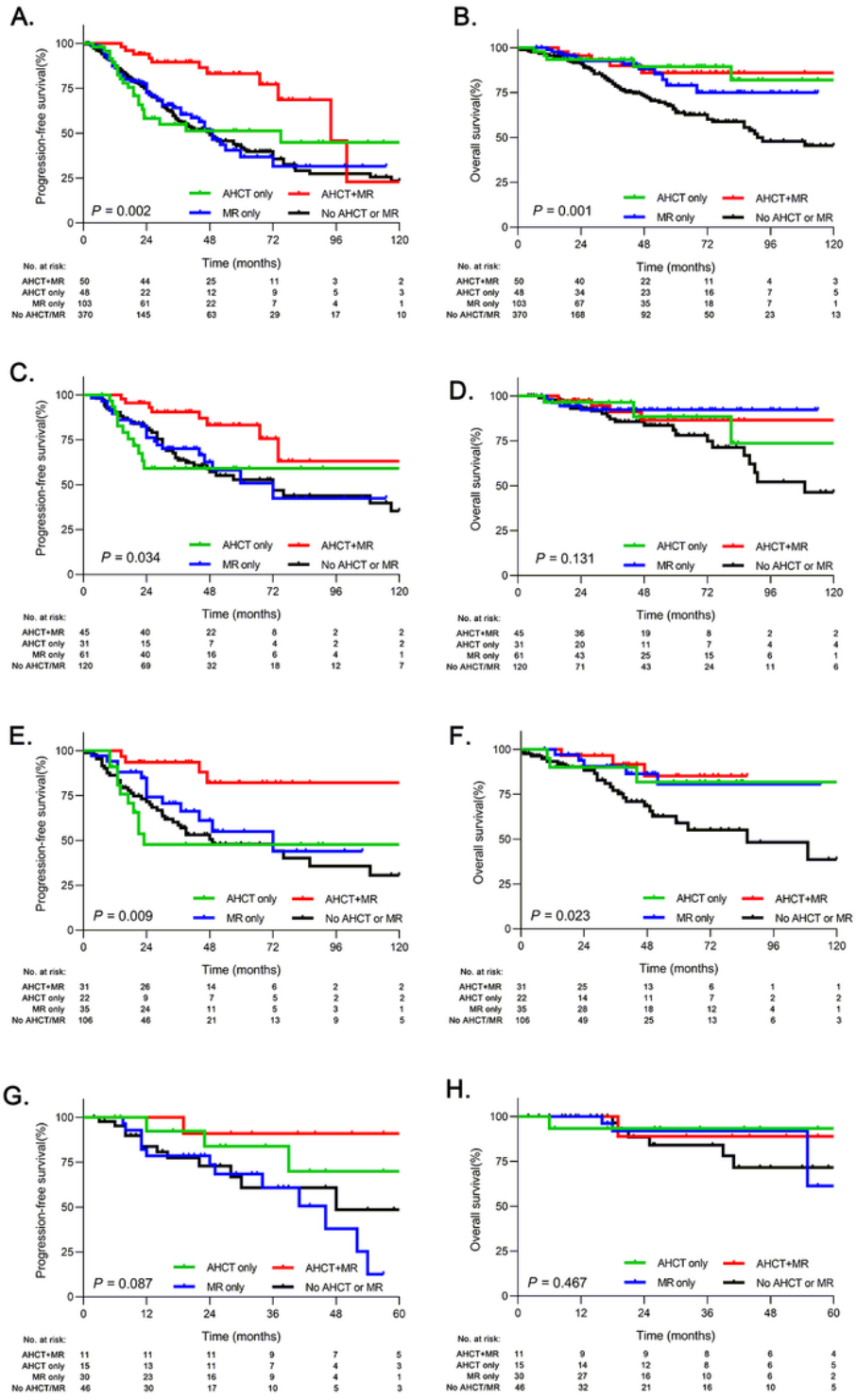

Figure 1

Survival curves according to frontline consolidated treatment.

Progression-free survival (PFS) and overall survival (OS) curves of patients responding to rituximab-containing induction **(A, B)**, achieving complete remission after rituximab-containing induction **(C, D)**, responding to R-HD-AraC therapies **(E, F)** and responding to chemotherapy combined with novel agents

(G, H). **A.** $p = 0.922$ between MR only and AHCT only; $p < 0.001$ between MR only and AHCT+MR; $p = 0.005$ between AHCT only and AHCT+MR; $p = 0.789$ between MR only and neither; $p = 0.763$ between AHCT only and neither; $p < 0.001$ between AHCT+MR and neither. **B.** $p = 0.481$ between MR only and AHCT only; $p = 0.530$ between MR only and AHCT+MR; $p = 0.611$ between AHCT only and AHCT+MR; $p = 0.010$ between MR only and neither; $p = 0.008$ between AHCT only and neither; $p = 0.026$ between AHCT+MR and neither.

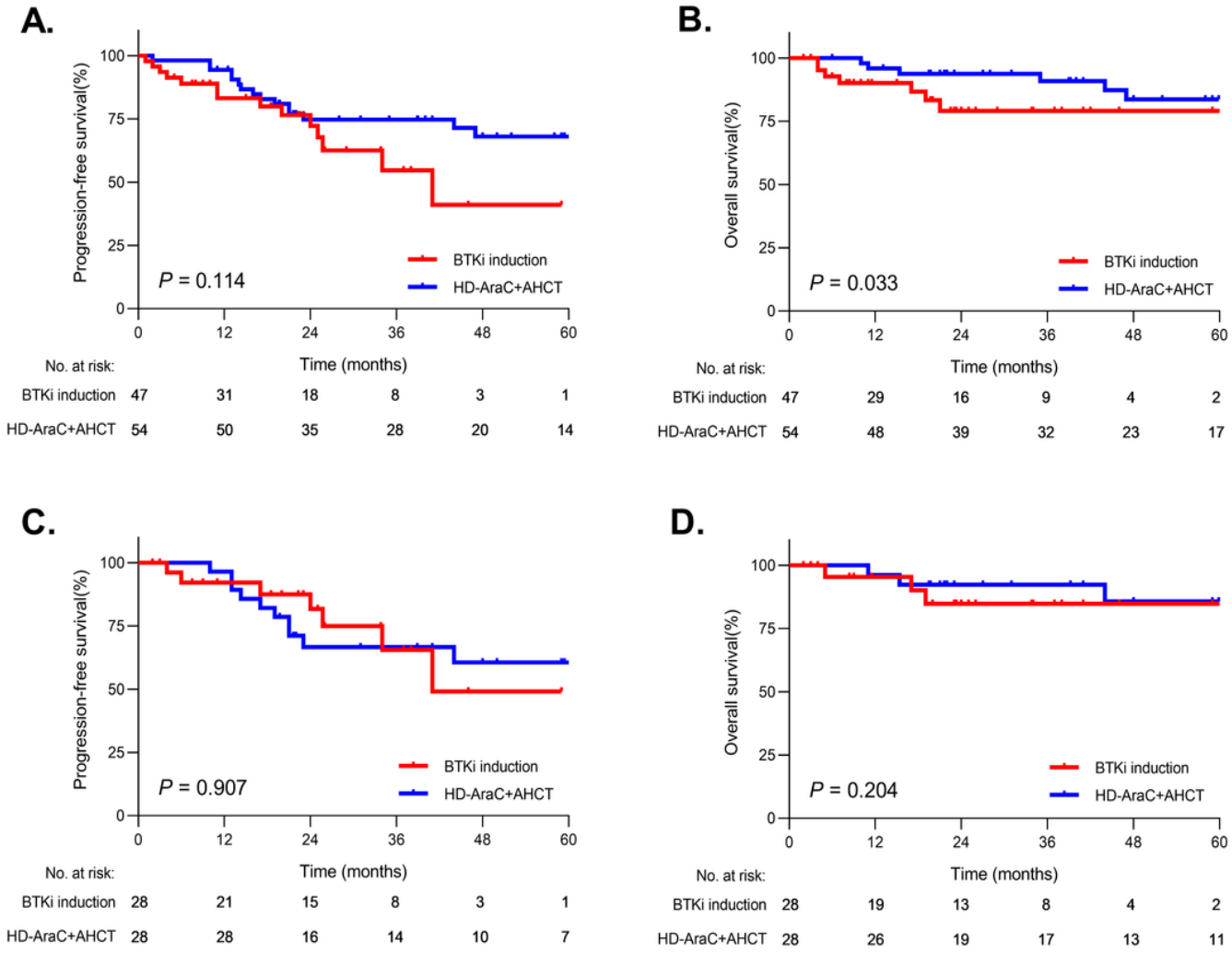

Figure 2

Survival curves according to the use frontline BTKi/cytarabine and consolidated AHCT.

Progression-free survival (PFS) and overall survival (OS) curves of patients treated with R-HD-AraC regimens followed by consolidated AHCT and BTKi combined with non-HD-AraC chemotherapy without AHCT consolidation in unadjusted analysis **(A, B)** and analysis after propensity score matching **(C, D)**.

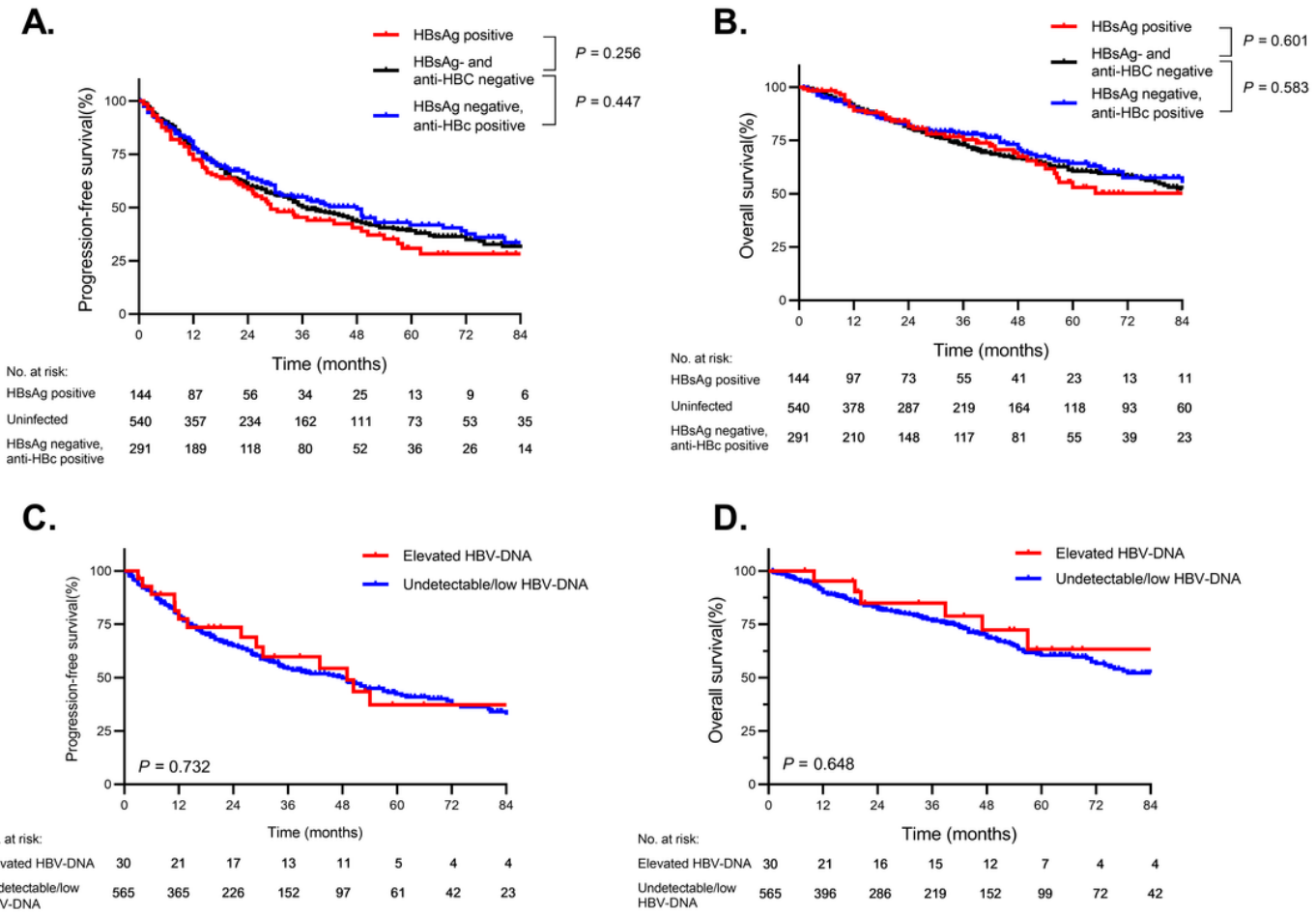

Figure 3

Survival curves according to hepatitis B virus (HBV) infection status and serum HBV-DNA level.

Progression-free survival (PFS) and overall survival (OS) curves of HBsAg-positive versus HBsAg-negative, anti-HBc–positive versus HBsAg- and anti-HBc–negative patients **(A, B)** and patients with high versus undetected or low serum HBV-DNA level **(C, D).**

Supplementary Files

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