Predicting Survival for Nasopharyngeal Carcinoma: Development and Validation of Nomograms With Routine Hematological Biomarkers Based on the 8th Edition of AJCC/UICC Staging System

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Research

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Abstract

Background

The 8th edition of AJCC/UICC TNM staging system (TNM system) and the previous nomograms have limitations, therefore we aimed to develop and validate nomograms incorporating routine hematological biomarkers with or without EBV DNA for overall survival (OS) and progression-free survival (PFS). We also evaluated the prognostic role of EBV DNA.

Material and Methods

1203 patients at our hospital from 2013 to 2016 were retrospectively reviewed and divided into two parts (922 patients for primary cohort and 281 for validation cohort). Nomograms (nomogram with or without EBV DNA) were developed and compared with other models (TNM system alone, TNM system with EBV DNA), via comparison the prognostic role of EBV DNA was evaluated. Internal and external validation were performed. Risk stratification were conducted with recursive partitioning analysis.

Results

The nomograms with EBV DNA for OS and PFS included sex, age, T category, N category, EBV DNA, albumin, neutrophil to lymphocyte ratio and lactate dehydrogenase. The nomograms without EBV DNA for OS and PFS included the same variables but without EBV DNA. The C-index for nomogram with EBV DNA was 0.715 for OS and 0.705 for PFS. For nomogram without EBV DNA, it was 0.709 and 0.700, respectively. It was 0.639 and 0.636 for TNM system alone and 0.648, 0.646 respectively for TNM system with EBV DNA. The nomograms with or without EBV DNA had better performance than both the TNM system alone and TNM system with EBV DNA, while the TNM system with EBV DNA were better than TNM system alone. The validation cohort indicates great applicability of nomograms. The patients were stratified into 4 risk groups.

Conclusion

The nomograms with or without EBV DNA provide better prognostication than the TNM system and also the TNM system with EBV DNA. EBV DNA is valuable in predicting survival, but it is not suggested to incorporate EBV DNA alone to TNM system.

Background

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma arising from the nasopharynx with unique unbalanced global distribution(1). It is endemic in east and southeast Asia and according to the Global Cancer Statistics, there would be 129,079 new cases and 72,987 deaths in a year(2). It is important to predict survival in NPC, the currently primary method is the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) Tumor-Node-Metastasis staging system (TNM system). However, despite of being updated to an 8th version lately, The TNM system is still insufficient due to the

limitation that it is confined to almost only anatomic information(3). For more accurate outcome prediction, incorporating more nonanatomic predictors is necessary.

Among numerous nonanatomic predictors, the hematological biomarkers have attracted widespread interest. They are not only effective, but also simple, low cost and easy to apply in clinical practice, which makes them ideal candidate predictors to refine the TNM system. Such hematological biomarkers mainly include systematic inflammation indices (neutrophil to lymphocyte ratio (NLR), platelets to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR)), nutritional indices (hemoglobin (Hgb), albumin (Alb)), and biomarkers related to cancer burden (lactate dehydrogenase level (LDH), alkaline phosphatase (ALP)), and serum ferritin (SF). A noteworthy biomarker is the plasma EBV DNA, on one hand, it is speculated to play a crucial role in NPC(4, 5), so it should be evaluated when the TNM system is refined; but on the other hand, EBV DNA is not available in many hospitals, therefore, it would be convenient if we create another refining version of TNM system without EBV DNA.

And here came the problem that how could we incorporate these biomarkers with the TNM system effectively? The nomogram is beneficial here. It could incorporate more variables via combination with statistical model, moreover, it is able to generate individualized prognostication and present a result in a simple graphical way(3, 6). It meets the need of the era of personalized and precision medicine. In fact, it is demonstrated to outperform the TNM system in many cancers(7, 8). There were also nomograms for NPC, however, most of them have drawbacks–ie, they were based on the outdated 7th TNM system(9), or used the problematic models(10); their applications have been limited.

Therefore, we developed and validated advanced, simple, cost-effective nomograms based on the 8th TNM system, covering the routine hematological biomarkers with or without EBV DNA. The nomograms focus on the overall survival (OS) and progress-free survival (PFS) for NPC patients at diagnosis, and were then compared with the 8th TNM system alone and the TNM system with EBV DNA. Via the comparison, the special roles of EBV DNA were evaluated. And to our knowledge, this is a first attempt to evaluate the role of EBV DNA in different multivariable models in the IMRT era for the prognostication of NPC.

Materials And Methods

Patients

This was a retrospective observational study in the real world, it enrolled 1203 patients with NPC diagnosed at our hospital during January 2013 and December 2016. The inclusion criteria were as follows: (1) patients with newly diagnosed, histologically confirmed non-metastatic NPC, (2) with completed intensity-modulated radiotherapy (IMRT), (3) with sufficient clinical data. The exclusion criteria were the following: (1) patients with other tumors, (2) patients with primary disorders from hematological or immune system. The study was approved by the ethics committee of our hospital and was reported

following the Statement of TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis)(11).

Diagnosis and collection of pretreatment information

The diagnosis was based on a detailed history, a complete physical examination, a pathological nasopharyngeal biopsy with fiberoptic nasopharyngoscopy, a pretreatment blood test, and other routine investigation including a magnetic resonance imaging (MRI) scanning from the suprasellar cistern to the collarbone, a computed tomography (CT) or radiography for chest, a CT or sonography for abdomen, a whole-body scan for bone, or a whole-body 18F-Fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT). By reviewing the electronic medical records, baseline information and data from blood test were collected, which included age, sex, the neutrophil count, the lymphocyte count, the monocyte count, the platelet count, Hgb, Alb, LDH, SF, and plasma EBV DNA. All patients were re-evaluated and re-staged according to the 8th TNM system carefully by two experienced oncologists separately.

Treatments

All patients' treatment strategies were based on the National Comprehensive Cancer Network Guidelines (NCCN Guidelines), so they received radiotherapy with or without chemotherapy, which mainly depended on the stage groups in the TNM system. As for radiotherapy, all patients completed the IMRT, in which the target volume was delineated as suggested by the International Commission Radiological Units Guidelines and the prescription dose and the plan evaluation was adjusted according to the Radiation Therapy Oncology Group Guidelines. As for chemotherapy, it included induction chemotherapy, concurrent chemotherapy and adjuvant chemotherapy. In induction chemotherapy, the main regimens were TPF (docetaxel [60 mg/m2 on day 1] and cisplatin [60 mg/m2 on day 1] and 5-fluorouracil [600 mg/m2, continuous intravenous infusion during 120h], repeated every 3 weeks, normally 2 or 3 cycles); In concurrent chemotherapy, cisplatin (100 mg/m2 every 3 weeks, normally 2 or 3 cycles) was adopted. In adjuvant chemotherapy, PF (cisplatin [80 mg/m2] and 5-fluorouracil [600 mg/m2, continuous intravenous infusion during 120h], repeated every 3 weeks, normally 2 or 3 cycles) was mainly used.

Follow up

Patient were evaluated every 3 months in the first 2 years after complete treatment, every 6 months in the following 3 years and then annually until death. At each follow-up visit, a detailed history, a complete physical examination, and other necessary examination which were similar to pretreatment evaluation were performed. When suspected recurrence case occurred, supplementary examinations such as nasopharyngeal biopsy were further required. The OS and PFS describe the prognosis of the NPC patients. The OS was calculated from the first date of treatment to the date of death from any cause; while the PFS was to the date of first recurrence or death from any cause, whichever came first.

Statistical analysis

The patients were divided into two parts, the former part from 2013 to 2015 was used as a primary cohort to develop nomograms, as the latter part from 2016, in which patients and treatment were more similar to ones that could potentially benefit from nomograms today, was used as a temporal external validation cohort(12, 13).Effective and routinely available variables (baseline information (age, sex), results from blood test (NLR, PLR, LMR, Hgb, Alb, LDH, SF, EBV DNA), T category and N category), which were reported by previous publication, were served as potential predictors. The NLR, PLR, and LMR was computed according to their definition. Categorical variables were defined from clinical findings while continuous variables were kept in a continuous form after a confirmation of linearity. EBV DNA were computed to categorical variables on the bias of a cut-off value. Variables inclusion followed Harrel's Guideline, in which suggested that the number of predictors should be no more than ten times the number of events(12, 14).

Survival outcomes (OS and PFS) were calculated via Kaplan-Meier method. In the primary cohort, the final prediction models were determined by the Cox proportional hazards model, in which variables reached a $p < 0.10$ in univariable analyses were further adopted in multivariable analyses after tests for proportional hazards assumptions. The multivariable analyses was performed with the Akaike information criterion(15) with a backward stepdown selection, which allows assessment for all variables and could consider all correlation between variables. Regarding the special role of EBV DNA, the cox analyses were conducted with or without EBV DNA separately, and based on the results, nomograms with or without EBV DNA were developed for OS and PFS. The performance of nomograms was evaluated in discrimination, calibration, and the clinical usefulness. Discrimination was assessed via Harrell' concordance-index (C-index), the C-calibration was assessed by a calibration plot, and the clinical usefulness was evaluated by the decision curves (DC)(16). To ensure the stability of the nomograms, internal validations were performed via bootstraps with 1000 resamples, examining and correcting the amount of overfitting(17). After development and internal validation, the nomograms were compared with each other and with TNM system alone, and with the model of TNM system with EBV DNA. The comparisons were assessed by the log likelihood ratio tests(17, 18). To better understand the correlation among them, their discrimination, calibration, and clinical usefulness were evaluated. In the external validation cohort, the generalizability of the nomograms was further assessed. First the total points of each patients were computed according to the corresponding nomogram; next, based on the total points, cox analyses were performed, providing survival estimating by the corresponding nomograms; finally, the performance of nomograms in the validation cohort was evaluated. After development, internal and external validation of the nomograms, the patients were stratified into different risk groups by the recursive partitioning analysis(19) on the bias of their points computing from nomograms.

The cut-off values were generated from X-tile. The transformations of variables were conducted in SPSS (Statistical Package for the Social Science) 25.0 for Windows, and other statistical analyses were computed with R version 3.6. All tests were two-sided, and $P < 0.05$ was considered to be statistically significant if not be noted particularly.

Results

Clinical characteristic and survival

There were 1203 patients in the study, with 922 patients in the primary cohort and 281 patients in the validation cohort, the clinical characteristics of the patients have been listed in Table 1. In the primary cohort, the median follow-up times was 52 months (range = 2–76 months), while it was 33 months (range = 2–40 months) in the validation cohort. The 3-year and 5-year OS was 87.9%, and 80.1% in the primary cohort, while the 3-year OS was 86.2% in the validation cohort. As for PFS, the 3-year and 5-year survival was 87.2%, 79.4% in the primary cohort and the 3-year survival was 83.1% in the validation cohort.

The development of nomograms

The nomograms were developed on the bias of the multivariable analyses. To determine variables for multivariable analyses, univariable analyses were firstly performed, and it was found that the proportional hazards assumptions were satisfied, and all of the 13 variables were associated with the OS and PFS. Next, multivariable analyses for OS and PFS were applied separately, and the results were shown in Fig. 1a, Fig. 1b, Fig. 1c and Fig. 1d. Based on the results, four nomograms were generated: two of them were nomograms with EBV DNA for OS and PFS (Fig. 2a, Fig. 2b), their predictors included sex, age, T category, N category, EBV DNA, Alb, NLR, LDH; other two were nomograms without EBV DNA for OS and PFS (Fig. 2c, Fig. 2d). Without EBV DNA, they contained the same predictors as the ones in nomograms with EBV DNA (sex, age, T category, N category, Alb, NLR, LDH).

The discrimination, calibration and clinical usefulness for nomograms, and their comparison with TNM system and with TNM system with EBV DNA

The 4 nomograms mentioned above, TNM system alone and TNM system with EBV DNA were compared with each other (Table 2), the result indicated that for both OS and PFS, the nomograms with EBV DNA are superior than others, the nomograms without EBV DNA come next, and then the TNM system with EBV DNA follows, while the TNM system alone has the poorest result.

The discrimination, which is the ability to distinguish patients who have an event and those who do not at a time, was measured by C-index. The C-index ranged from 0.5 (no better than chance) to 1.0 (perfect discrimination). The value of C-index for each model were listed in Table 2, and it was visually shown in Fig. 3a and Fig. 3b. The nomogram with EBV DNA had the highest C-index both for OS and PFS, while the 8th TNM system had the lowest.

Calibration evaluates how close the model estimated risk is to the actual observed risk, and it could be depicted by a calibration plot. As Fig. 4a and Fig. 4b shows, all models had good agreements between estimated risk and actual risk, and meanwhile, the nomogram with or without EBV DNA were better than the TNM system alone and the TNM system with EBV DNA.

Clinical usefulness assesses whether decisions derived from a model improve patient outcomes, and it could be depicted in a decision curve (DC). The DC's *x* axis is determined by the threshold probability, at which the harm of false-positive intervention exceeds the harm of a false-negative non-intervention and thus an intervention is triggered. And the *y* axis is determined by a net benefit. Net benefit is calculated by subtracting the relative costs, which is measured by the proportion of false-positive result weighted by a ratio from threshold probability, from the proportion of true-positive result. Therefore, at the same threshold probability, the higher a net benefit is, the better the clinical usefulness is. Figure 5a and Fig. 5b pictured the DC. The nomogram with or without EBV DNA outperformed the TNM system and the TNM system with EBV DNA, as the TNM system with EBV DNA was better than the TNM system alone.

The validation of nomograms

As shown in Table 2, the validation cohort indicated consistent improvement of nomograms to TNM system alone and TNM system with EBV DNA, as the TNM system with EBV DNA had better performance than the TNM system alone do. All the nomograms showed stably good agreement in the calibration plot. (Fig. 6a, Fig. 6b)

Risk stratification from nomograms

Risk stratification was conducted on the bias of the total points from nomograms, details are given in Table 3. Figure 7a, Fig. 7b, Fig. 7c, Fig. 7d showed the Kaplan-Meier curves for the 4 risk groups and statically significant difference was observed. To better understand how the nomograms differed from the TNM system in prognostication, bar plots were applied (Fig. 8a, Fig. 8b, Fig. 8c, Fig. 8d).

Discussion

The nomogram has shown its superiority over the TNM system in many cancers. Based on the 8th TNM system, we developed and validated advanced incorporating the hematological biomarkers for both OS and PFS in NPC patients at diagnosis, it is able to generate individualized prognostication and it is proved to be more sufficient than the current 8th TNM system, yielding advantage in facilitating individualized risk stratification and decision making. Moreover, it is simple, low cost and easy to apply in clinical practice. We also included EBV DNA in the study and evaluated the role of it in different multivariable models, and to our knowledge, this is a first attempt to evaluate EBV DNA in different multivariable models in the IMRT era for the prognostication of NPC.

There were nomograms for NPC in the recent years, and they demonstrated consistent superiority over the TNM system. However, it has been a pity that most of them were based on the outdated 7th TNM system(9, 20), as this makes prognostication difficult under the condition that the clinician must refer back to the 7th edition. Based on the 8th edition, few nomograms were set up, unfortunately, there were significant drawbacks. One common drawback was categorizing all continuous variables. Since it causes information loss and reduces accuracy, it has been long regarded as problematic, highly inefficient and unnecessary, and was strongly advised against by specialists(12, 21, 22). In a nomogram suggested by Xu et.al(10), for example, the variables were all dichotomized, the uncertainty of best cut-off values and

problem of overfitting should be under carefully evaluation. Another major drawback was the inappropriate consideration about potential variables. In the study of Pan et.al, they neglected the importance of EBV DNA and inflammation risk factors which were widely accepted as crucial predictors nowadays, and they failed to develop nomogram for PFS(23); Sun et.al built up the model with merely TNM system and EBV DNA(24), but as the present study indicated, this combination might not be effective enough, more variables should be contained.

The nomograms proposed in this study was based on the current 8th TNM system and they kept variables continuous as far as possible to avoid unnecessary information loss, moreover, they included crucial potential predictors which is widely accepted and routinely available in most of the hospitals. Regarding the special role of EBV DNA, they developed nomogram with or without it. Due to their simple yet cost-effective character, they provided more probabilities for a further large-scale validation and a widely acceptance and application, benefiting individualized risk stratification, clinical decision making and proper surveillance.

Numerous studies indicated that the hematological biomarkers are effective in predicting survival outcomes for NPC patients. NLR, PLR, LMR, as the representation of inflammation in vivo which plays important role in tumor development, they are closely linked to the prognosis(25, 26). Low level of Hgb implies poor cancer oxygenation status and are associated with the poorer survival(27, 28). SF and ALP is proved to be an adverse prognostic factor(29, 30), as a high Alb indicates enough nutrition in human body and is of positive prognostic importance(31). LDH were reported to be of great value in measuring the tumor burden in the NPC and were efficient in estimating outcomes(32). Baseline information in the present study (sex, age) and the TNM system (T category, N category) had been long used in predicting survival outcomes. Other potential biomarkers, such as epidermal growth factor receptor (EGFR), microRNAs, are expensive, technically difficult to some extent, and not routinely available in some hospitals, so they were ruled out in this study, as our aim is to develop nomograms that are simple, cost-effective and easy to apply.

Meanwhile, the special role of the plasma EBV DNA is noteworthy. On the one hand, the EBV infection is common causal agent of NPC and the EBV DNA are used to screening and diagnosis(5), in fact, it has become the first and the only nonanatomic factors to be included in the 8th edition of TNM system. There were also many studies indicating that adding EBV DNA to the TNM system(4), or even it alone(20) could result in more accurate prognostic prediction than the TNM system. But how important it is indeed and whether it is better than the combination of other prognostic biomarkers remained unknown. On the other hand, the test for EBV DNA has not been available in many hospitals, and in the hospital that could perform such test, interlaboratory variability occurs for lacking of globally methodology standardization(33). Taken these together, we developed nomograms with or without EBV DNA, the model of TNM system with EBV DNA, and compared them with each other and with the TNM system in order to evaluate the importance of EBV DNA and also to provide a more available nomogram without EBV DNA. The comparison indicated that all three models incorporating nonanatomic factors with the TNM system are more accurate and of better clinical usefulness than the TNM system alone, which is in accordance

with the previous studies(20) in NPC in the past era of two-dimensional conformal radiotherapy. And the result also demonstrated that while the nomogram with EBV DNA rank first in the prognostication for patients as we supposed, the nomogram without EBV DNA outperformed the combination of TNM system and EBV DNA. This is meaningful considering the fact that some hospitals are not able to perform tests for EBV DNA and the methodology of testing it has not been globally standardized yet. The result indicated an outstanding advantage and a promising future for nomogram without EBV DNA. It also indicated that EBV DNA was a stable prognostic predictor for NPC, incorporating it with other variables to TNM system is of value, however it was not suggested to incorporate EBV DNA alone.

The nomograms confirmed their superiority in the validation cohort. A higher C-index and a good agreement in the calibration plot demonstrated their robustness and generalizability in application. To better facilitate clinical decision making and proper surveillance, we further stratified patients into different risk groups. The stratification should be valuable in initial decision making before individualization and in the design for future clinical trial.

Despite that the nomograms have many advantages over the TNM system and benefit the clinical practice, there were some limitations. First, as a retrospective study, there might be potential selection bias. Second, it was from a single center in high risk area. Third, the nomograms did not include C-reactive protein as a potential biomarker, however it could be argued that C-reactive protein is not routinely available in most of the hospitals now and is not always consistently associated with the survival. Four, validated in the temporal cohort indicated the robustness and generalizability of nomograms, inevitably, they needs more validation in other areas and at other time to further prove their transportability before widely application(12). The first step of validation is taken here and more will be carried out in the near future.

Conclusions

Based on the 8th AJCC/UICC TNM staging system for patients with NPC, we developed and validated nomograms incorporating routine hematological biomarkers with or without EBV DNA for both 5-year OS and PFS. The nomograms with or without EBV DNA provide better prognostication than the TNM system alone and also the combination of TNM system with EBV DNA. The nomograms are simple, cost-effective, and easy to apply. No matter whether EBV DNA is available in the hospital or not, they could offer practical tools for sufficient individualized prognostication, providing more accurate patient counseling, benefiting clinical decision-making and tumor surveillance. To promote application of the nomograms, more validation in different areas and at different time are in need. EBV DNA was a stable prognostic predictor for NPC, incorporating it with other variables to TNM system is of value, however it was not suggested to incorporate EBV DNA alone.

Abbreviations

NPC, Nasopharyngeal carcinoma;

AJCC/UICC, the American Joint Committee on Cancer/Union for International Cancer Control;

TNM system, Tumor-Node-Metastasis staging system;

PLR, platelets to lymphocyte ratio;

LMR, lymphocyte to monocyte ratio;

NLR, neutrophil to lymphocyte ratio;

LDH, lactate dehydrogenase level;

Alb, albumin;

SF, serum ferritin;

Hb, hemoglobin;

ALP, alkaline phosphatase;

EBV DNA, Epstein-Barr virus DNA;

OS, overall survival;

PFS, progress-free survival;

IMRT, intensity-modulated radiotherapy;

TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis;

MRI, magnetic resonance imaging;

CT, computed tomography;

PET/CT, positron emission tomography and computed tomography;

NCCN, the National Comprehensive Cancer Network;

C-index, Harrell' concordance-index;

SPSS, Statistical Package for the Social Science.

Declarations

Ethics approval and consent to participate

The study was in accordance with the Declaration of Helsinki and was approved by the ethics committee of Guangxi Medical University Cancer hospital. Patient consent to review their medical records was not applicable due to the retrospective nature of the study, and the research involved no more than minimal risk to the participants. The data were anonymously analysed. All the participants' personal information is confidential.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design: XDZ, YL; data collection and

data analysis: YL, KHC, JY, JZ, RRP, DSS, CY, SQ, and LL; Manuscript writing and supervision: YL, XDZ, KHC. All authors read and approved the final manuscript.

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Tables

Table 1. Patient demographics and clinical characteristics		
Characteristic	All Patients	Primary cohort
Total, No. (%)	1203 (100.0)	922 (76.6)
Age, y		
Median (range)	47 (12, 79)	46 (12, 79)
Mean	46.40	46.10
Sex, No. (%)		
Male	877 (72.9)	596 (72.9)
Female	326 (27.1)	254 (27.5)
T category, No. (%)		
T1	66 (5.5)	46 (5.0)
T2	432 (35.9)	321 (34.8)
T3	410 (34.1)	343 (37.2)
T4	295 (24.5)	212 (23.0)
N category, No. (%)		
N0	70 (5.8)	45 (4.9)
N1	625 (52.0)	465 (50.4)
N2	400 (33.3)	341 (37.0)
N3	108 (9.0)	212 (23.0)
Stage, No. (%)		
	22 (1.8)	13 (1.4)
	298 (24.8)	218 (23.6)
	502 (41.7)	420 (45.6)
A	381 (31.7)	271 (29.4)
EBV DNA, No. (%)		
<8030	914 (76.0)	727 (78.9)
≥8030	289 (24.0)	195 (21.1)
PLR		

Median (range)	147.1 (34.42, 308.85)	149.21 (34.42,308.85)
Mean	153.86	154.08
LMR		
Median (range)	4.13 (0.19, 8.84)	4.11 (0.19,8.73)
Mean	4.24	4.19
NLR		
Median (range)	2.208 (0.79, 5.17)	2.25 (0.78,5.18)
Mean	2.31	2.34
LDH		
Median (range)	176.0 (95.0, 300.0)	178.6 (100.0,300.0)
Mean	179.50	181.90
Alb		
Median (range)	42.8 (32.8, 53.5)	43.5 (32.8,53.5)
Mean	42.90	43.50
SF		
Median (range)	276 (1, 774)	281 (115,774)
Mean	293.60	294.00
Hb		
Median (range)	139 (95, 180)	139 (95,180)
Mean	138.30	138.00
ALP		
Median (range)	66 (24, 119)	64 (24,119)
Mean	67.36	65.30
Treatment, No. (%)		
Chemoradiotherapy	1072 (89.1)	834 (90.5)
Radiotherapy	131 (10.9)	88 (9.5)
Abbreviation: PLR, platelets to lymphocyte ratio; LMR, lymphocyte to neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase level; Alb, hemoglobin; ALP, alkaline phosphatase.		

Figures

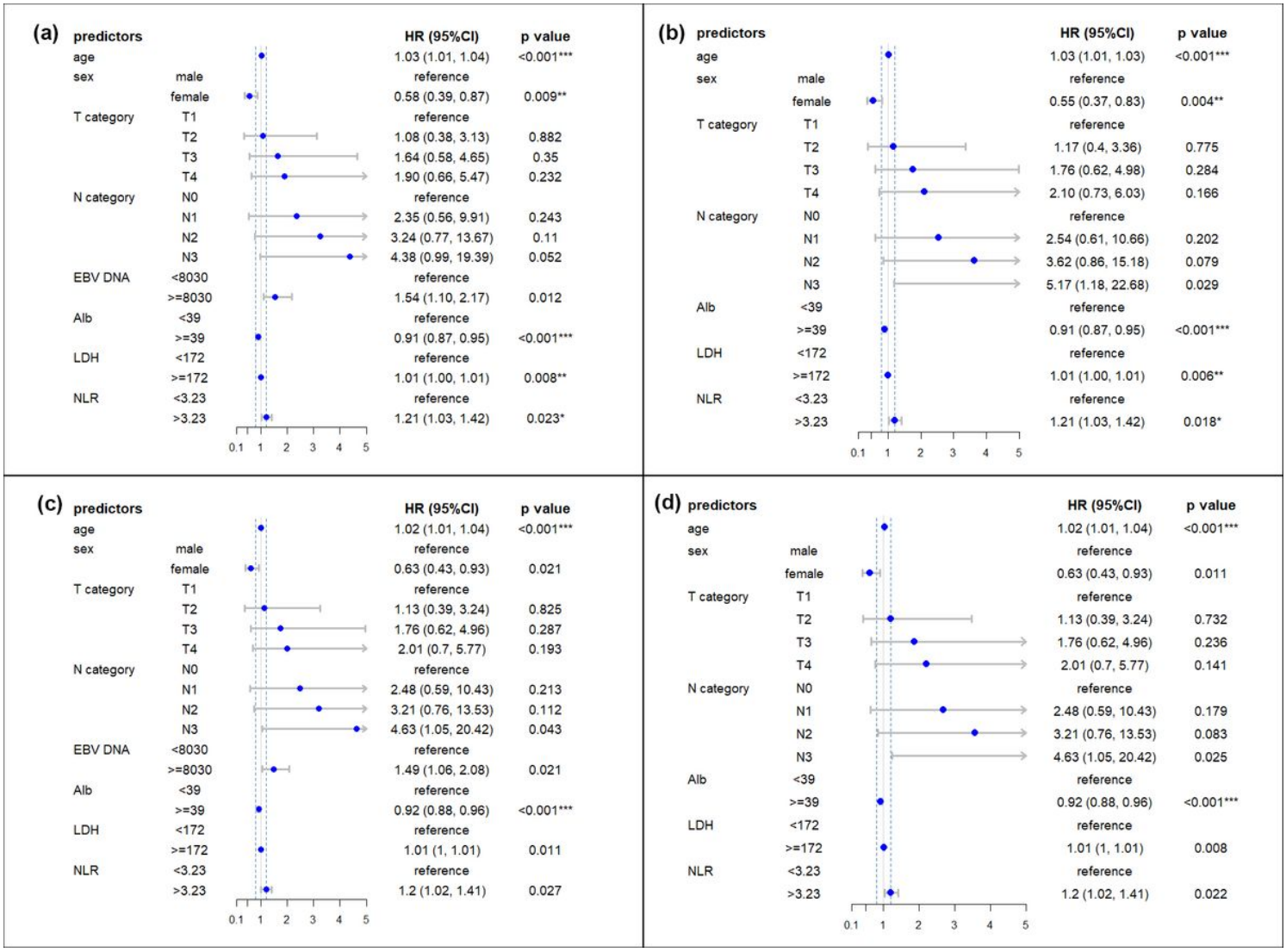

Figure 1

Forest plots from the results of multivariable analyses for OS with EBV DNA (a), OS without EBV DNA (b), PFS with EBV DNA (c), and PFS without EBV DNA (d). Abbreviation: HR, hazard ratio; CI, confidence interval; Alb, albumin; LDH, lactate dehydrogenase level; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progress-free survival.

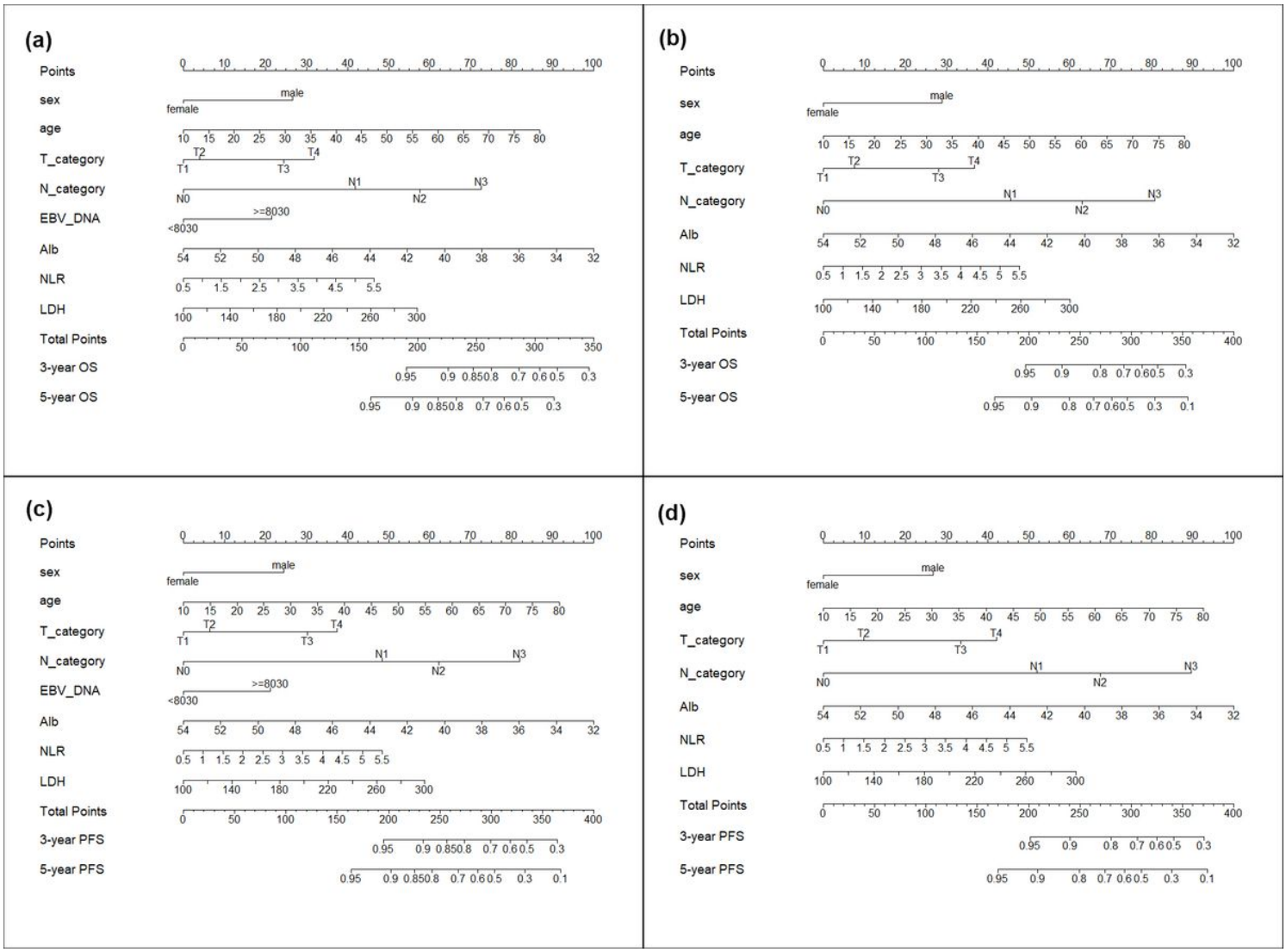

Figure 2

Nomograms. (a) nomogram with EBV DNA for OS, (b) nomogram without EBV DNA for OS, (c) nomogram with EBV DNA for PFS, (d) nomogram without EBV DNA for PFS. Note: The nomogram is used to predicted OS and PFS for an individual person. Usage: first, the top line “points” is corresponding with variables, draw a straight line up from any variable to the “point” and get to know the point of the variable. Second, sum up points of all variables and put it at the “total points” line. The “total points” is one-to-to corresponding with OS and PFS. Abbreviation: HR, hazard ratio; CI, confidence interval; Alb, albumin; LDH, lactate dehydrogenase level; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progress-free survival.

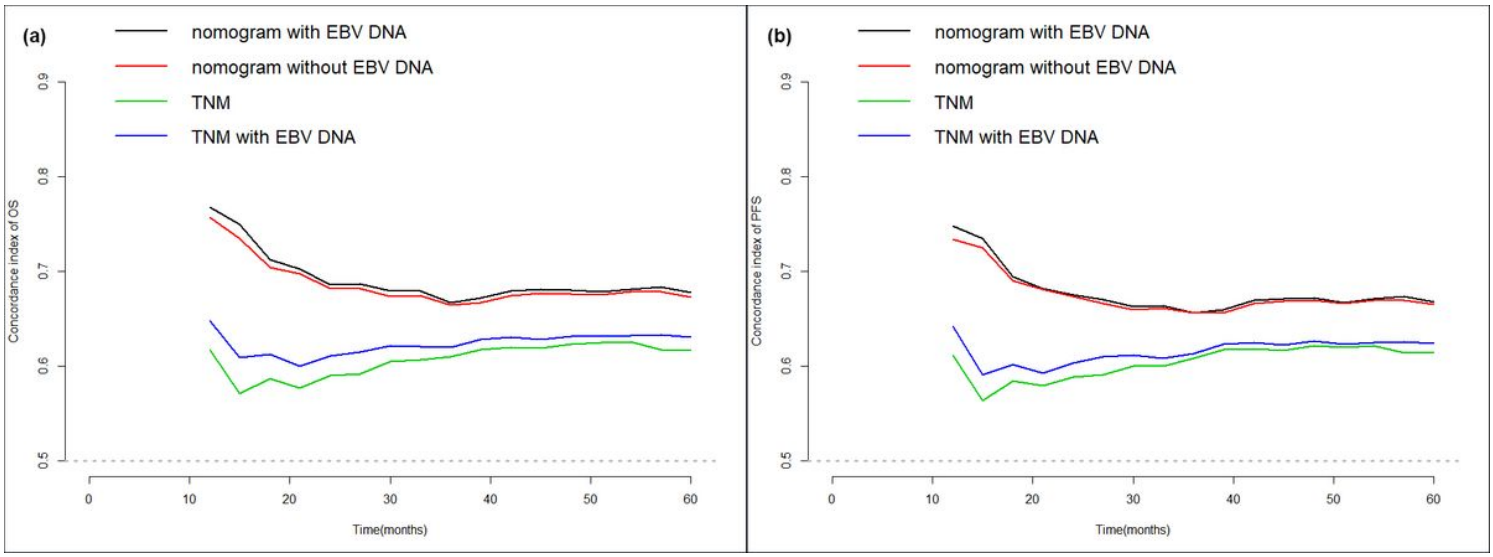

Figure 3

C-index for nomograms with or without EBV DNA, TNM system alone, TNM system with EBV DNA for OS (a) and PFS (b) in the primary cohort. Abbreviation: OS, overall survival; PFS, progress-free survival.

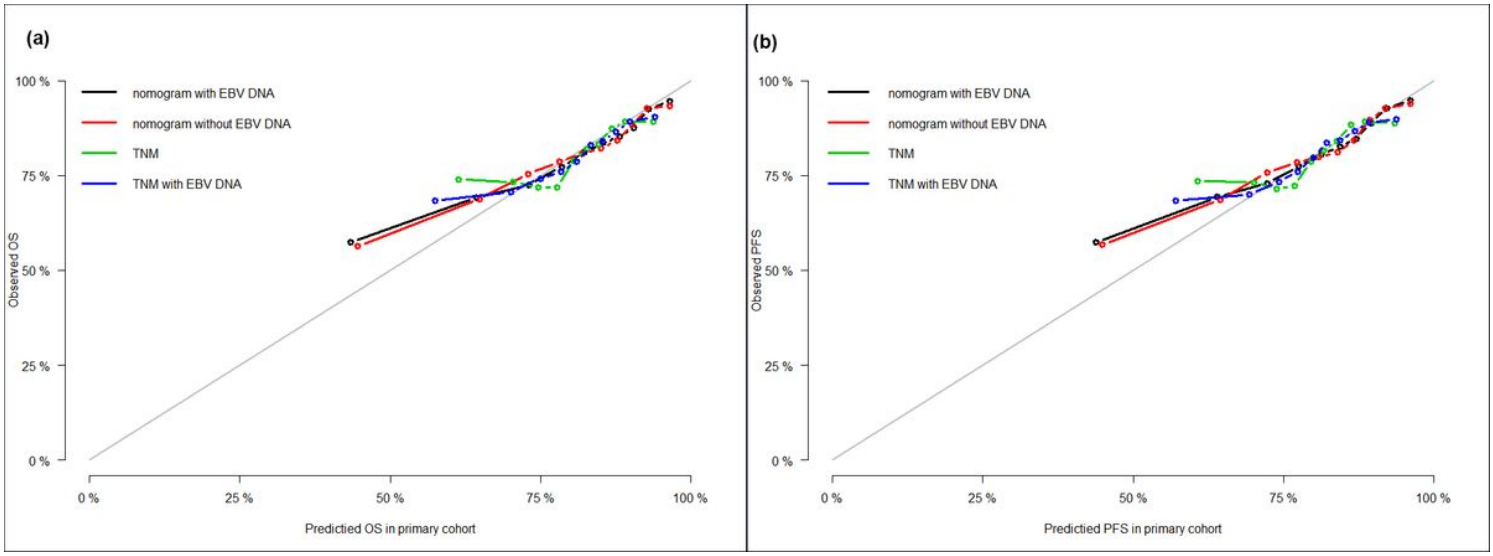

Figure 4

Calibration plots for nomograms with or without EBV DNA, TNM system alone, TNM system with EBV DNA of OS (a) and PFS (b) in the primary cohort. Abbreviation: OS, overall survival; PFS, progress-free survival.

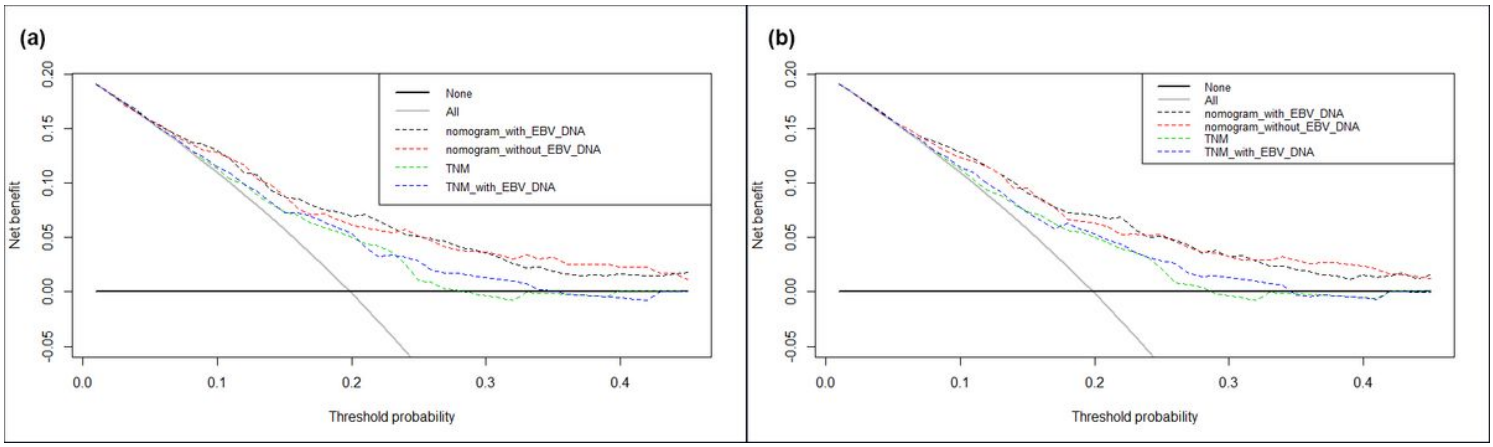

Figure 5

The decision curve for nomograms with or without EBV DNA, TNM system alone, TNM system with EBV DNA for OS (a) and PFS (b) in the primary cohort. Note: x axis is determined by the threshold probability, at which the harm of false-positive intervention exceeds the harm of a false-negative non-intervention and thus an intervention is triggered. And the y axis is determined by a net benefit. Net benefit is calculated by subtracting the relative costs (the proportion of false-positive result weighted by a ratio from threshold probability) from the proportion of true-positive result). Therefore, at the same threshold probability, the higher a net benefit is, the better the clinical usefulness is. Abbreviation: OS, overall survival; PFS, progress-free survival.

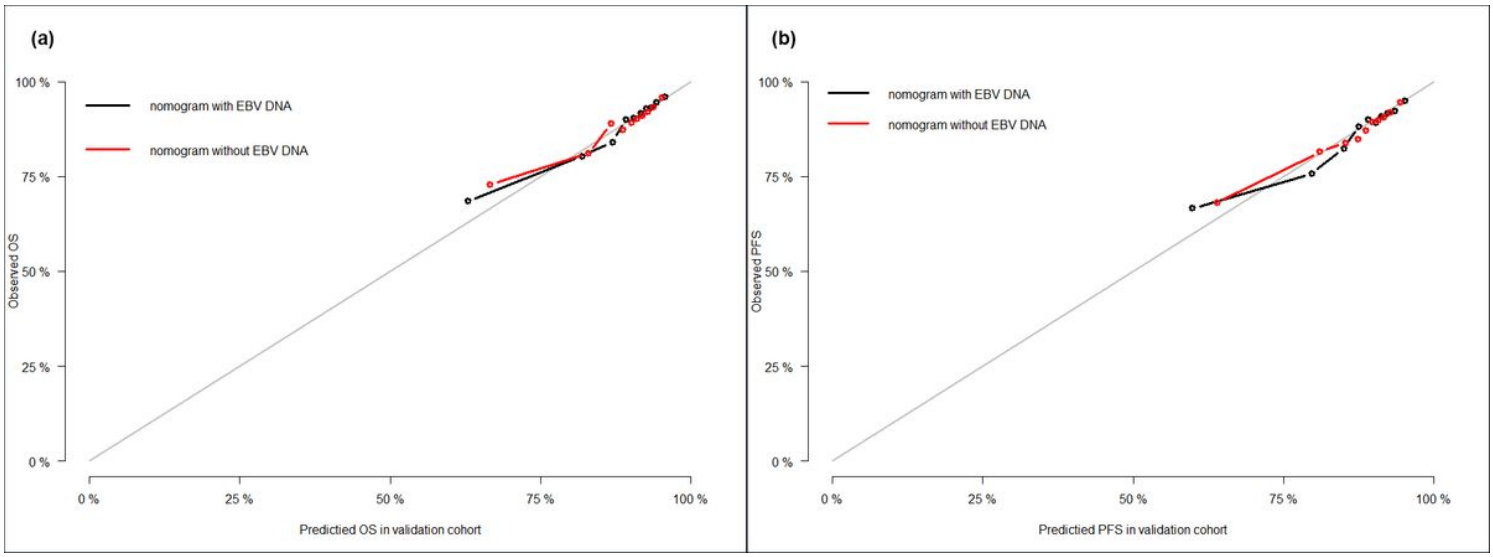

Figure 6

Calibration plots for nomograms with or without EBV DNA of OS (a) and PFS (b) in the validation cohort. Abbreviation: OS, overall survival; PFS, progress-free survival.

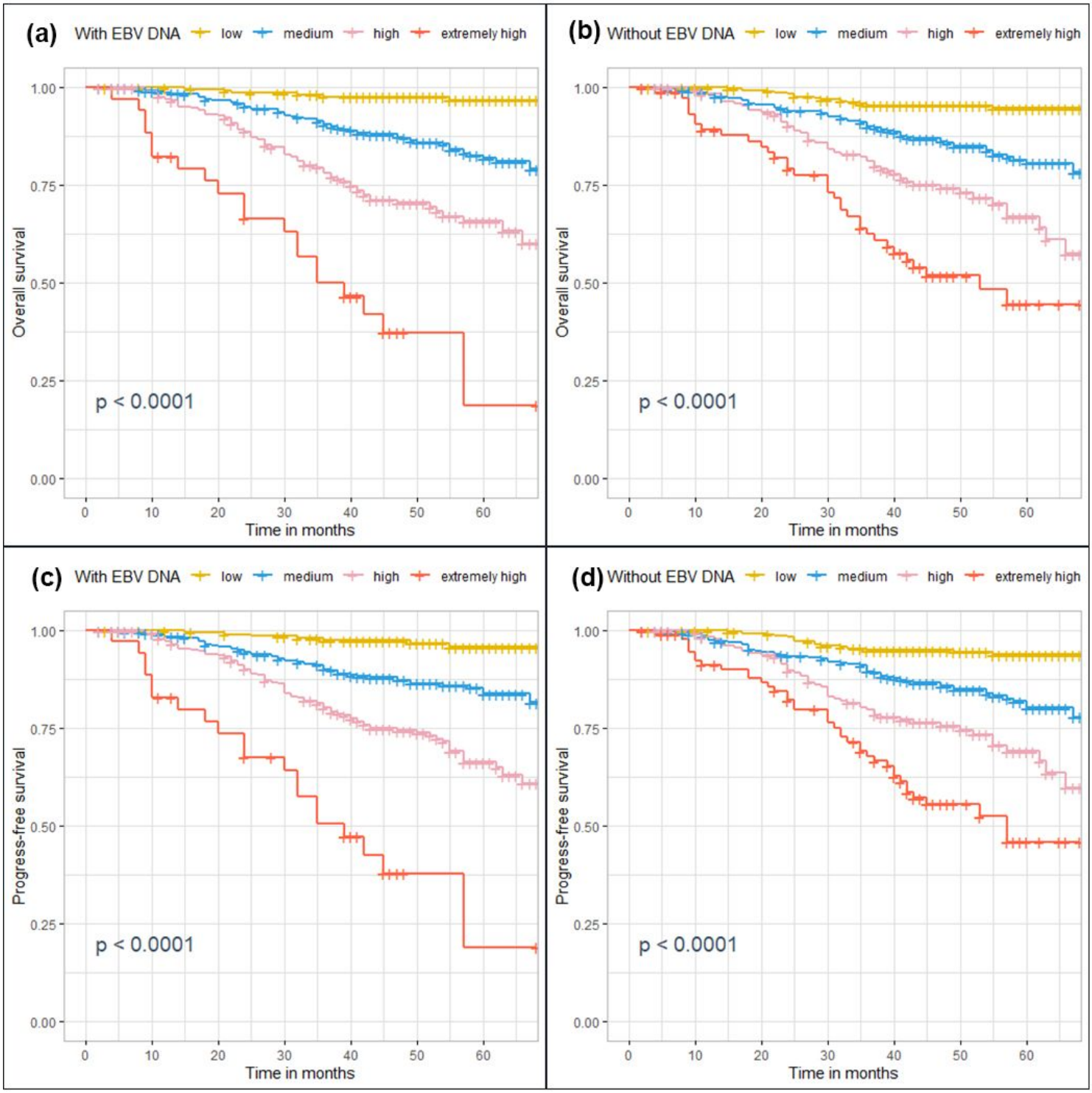

Figure 7

Kaplan-Meier plots for risk groups derived from (a) nomogram with EBV DNA for OS, (b) nomogram without EBV DNA for OS, (c) nomogram with EBV DNA for PFS, (d) nomogram without EBV DNA for PFS. Abbreviation: OS, overall survival; PFS, progress-free survival.

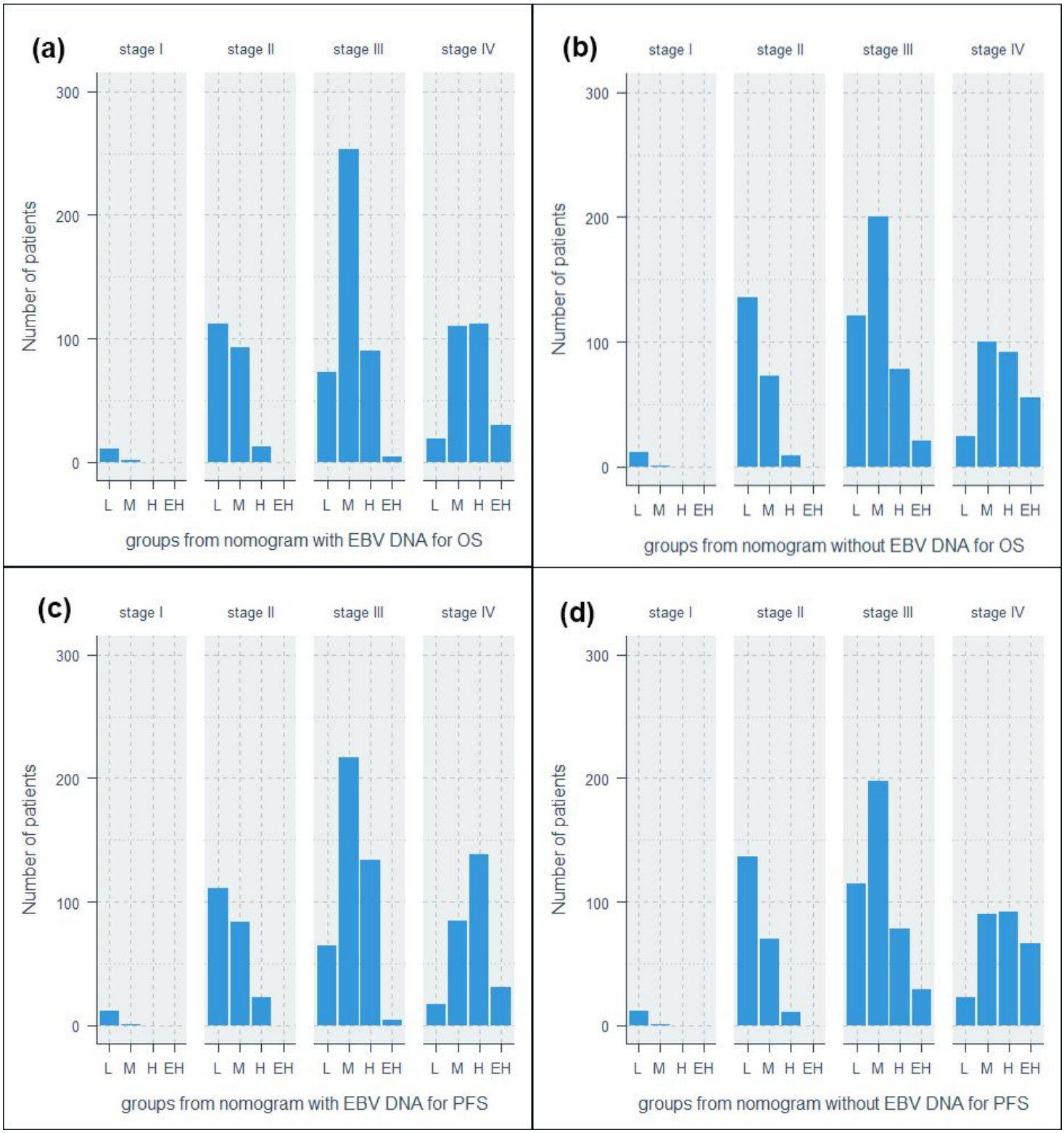

Figure 8

Bar plots depicting the distribution of risk groups in TNM system. (a) nomogram with EBV DNA for OS, (b) nomogram without EBV DNA for OS, (c) nomogram with EBV DNA for PFS, (d) nomogram without EBV DNA for PFS. Abbreviation: L, low risk; M, medium risk; H, high risk; EH, extremely high risk; OS, overall survival; PFS, progress-free survival.

Supplementary Files

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- Legendsoffigures.docx