Clinical Characteristics and Prognostic Factors of Anal Adenocarcinoma: A Nomogram Development Based on SEER Database and Validation in Real- World Study

Yu-Wen Zhou
West China Hospital of Sichuan University
Gui-Xia Wei
West China Hospital of Sichuan University
Lian-Sha Tang
West China Hospital of Sichuan University
Jia-Ling Wang
West China Hospital of Sichuan University
Meng Qiu (qiumeng@wchscu.cn)
West China Hospital of Sichuan University

Research Article

Keywords: Anal adenocarcinoma, Squamous cell carcinomas of the anal canal, Propensity-score matching, Prognostic factors, Nomogram

Posted Date: March 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1431356/v1

Abstract

Purpose: The purpose of this study was to comprehensively understand anal canal adenocarcinomas (AA) and develop a nomogram for prognostic prediction of AA.

Methods: Data were extracted from the Surveillance, Epidemiology and End Results (SEER) database (year 2004-2015). And real-world data was collected from West China Hospital (WCH) databases. Propensity-score matching (PSM) was performed to balance the demographic characteristic. A novel nomogram was developed to estimate individual survival probability and its performance was validated using the concordance index (C-index), calibration curves, and decision curve analyses (DCA).

Results: A total of 28,282 patients were enrolled including 749 AA patients and 7,152 squamous cell carcinomas of the anal canal (ASCC) patients. Before PSM, patients with AA had a shorter cancer specific survival (CSS) and OS than those with ASCC. However, after PSM, patients with AA were related to a favorable OS (p <0.001), but a comparable CSS (p =0.140) to those with ASCC. Age, sex, grade, surgery, and M stage were the independent prognostic factors of CSS for AA and were included in the establishment of novel nomogram. Patients from WCH database (n= 112) were used as external validation cohort. The C-index of the nomogram was 0.78 and 0.735 in internal and external validation, respectively, which suggested the good discrimination power of the model. Furthermore, calibration curves and DCA suggested good agreement between the predicted and actual survival. Lastly, a risk classification system based on nomogram revealed the reliability of the novel model.

Conclusion: AA and ASCC had distinct clinical features. AA was associated with a better prognosis than ASCC after PSM. The model of nomogram showed an accurate predictive ability for prognostic factors of AA patients.

Introduction

Anal canal adenocarcinomas (AA) is a rare disease, accounting for only 1% of gastrointestinal neoplasms[1]. Due to its rarity, the understanding of AA remained limited and the optimal treatment of AA is controversial. The current treatment of AA is based on that of rectal adenocarcinomas, using multimodal therapy with neoadjuvant chemoradiation followed by resection[2]. The primary pathological type of anal canal is squamous cell carcinomas, which accounts for approximately 85% of all neoplasms of anal canal[1]. Compared with squamous cell carcinomas of the anal canal (ASCC), AA frequently develop distant metastases and has a worse prognosis compared with ASCC[3, 4]. However, few studies have investigated the clinical and prognostic difference between AA and ASCC, and most of previous studies are case reports and small-scale retrospective studies.

Although, the TNM staging system is widely used in prognosis prediction for patients with cancer[5]. The prognosis of patients with AA varies with each individual, even at the same TNM stage. The survival of AA patients is associated with many factors including age, sex, the number of positive lymph nodes, radiation, chemotherapy, and radical surgery[6, 7]. No single variable can predict survival in AA accurately. Nomogram has been considered as a reliable tool which was widely used to predict and measure numerical probabilities for individual patients by incorporating and illustrating relevant factors[8, 9]. Some studies have confirmed that nomograms may be more precise to predict prognoses compared with traditional TNM staging systems[10, 11]. Besides, there was absent of explicit predictive factors of AA, for the first time, a nomogram was performed to predict the prognoses of AA by using data from the Surveillance, Epidemiology and End Results (SEER) database and real-world database. In our study, to obtain a comprehensive understanding of AA, we also applied a PSM and nomogram to analyze the clinical characteristic and prognostic variables of patients with AA.

Materials And Methods

Patients and data collection

This was a retrospective study based on the data from a publicly database, SEER registry program, which reports the cancer morbidity and survival rate from several regions that encompass approximately 30% of the US population[12]. Patients diagnosed with AA and ASCC between 2004 and 2015 in SEER 18 registries were enrolled in this study. AA was identified using the International Classification of Diseases for Oncology version 3 (ICD-O-3) site codes: C21.0 (anus, not otherwise specified), C21.1 (anal canal), C21.2 (cloacogenic zone), and C21.8 (overlapping lesion of rectum, anus, and anal canal). Morphology codes used in adenocarcinoma were 8140–8151, 8154–8231, 8243–8245, 8250–8576 and were 8000–8131, 8980–8981 in squamous cell carcinoma. And patients with incomplete data, survival time = 0, or diagnosed with a second malignancy were excluded.

The demographic traits (age, gender, race, marital status, tumor grade, T stage, N stage, M stage, metastatic sites), treatment strategies (surgery, chemotherapy, radiation) and survival information were obtained from SEER database. Age at diagnosis was classified as three categories:≤50, 50–70, and > 70 years. Race was divided four categories: white, black, other, and unknown (Other include American Indian/Alaskan native, and Asian/Pacific Islander, and others unspecified). But the detailed chemotherapy regimens and whether patients received combined therapies were not available. The primary outcome of this study were overall survival (OS) and cancer specific survival (CSS). OS was defined as the lifetime from confirmation diagnosis to die of any cause. CSS referred to death caused by the tumor.

PSM method

We used a 1:1 PSM strategy to match different patients with AA and ASCC in order to create well-matched cohorts and decrease possible confounding effects. Variables used for matching were age, sex, race, marital status, grade, T stage, N stage, M stage, bone metastasis, liver metastasis, brain metastasis, lung metastasis, chemotherapy, radiotherapy, and surgery, which were independent prognostic factors of the whole cohort according to the univariate and multivariate analysis. The nearest neighbor matching algorithm without replacement was performed to ensure adequate matches.

Nomogram and the validation method

Based on univariate, multivariate Cox proportional hazards model, as well as clinical experience to screen prognostic factors of AA patients to establish a novel nomogram. Patients with AA obtained from SEER databases with complete information were used to establish the nomogram prediction model and further applied as internal validation group, while patients from West China Hospital (WCH) databases were used as external validation group. Then we constructed the concordance index (C-index), calibration curves, and decision curve analyses (DCA) to measure the performance and accuracy of the established nomogram. Finally, a risk classification system was established based on the total scores of each patient in two cohorts using the nomogram. And all patients were divided into low-, intermediate-, and high-risk group, with trisection score values.

Statistical analysis

Patients' data were obtained from SEER*Stat software version 8.3.8 (https://seer.cancer.gov/seerstat). Statistical analysis was performed using SPSS version 25.0 (IBM Inc., Chicago, IL) and R version 4.0.3 (http://www.R-project.org). Categorical data were analyzed using the Chi-square test. Differences between CSS were analyzed by log-rank test, and survival curves were made by the Kaplan-Meier method. PSM was performed by using the nearest neighbor matching method with a caliper of 0.001 on the propensity scale with logistic regression. Cox proportional hazard regression models were performed to obtain adjusted hazard ratios (HRs) and 95% confidence interval (CI) to estimate probable risk factors for survival outcomes. The *p*-values < 0.05 were considered statistically significant.

Results

Baseline characteristics of the study cohort

A total of 28,282 patients were screened, 20,381 patients were excluded according to our exclusion criteria, ultimately, 7,901 patients were included in this study including 749 patients with AA and 7,152 patients with ASCC. After 1:1 PSM, 747 patients of each group were obtained (Supplementary Fig. 1). Baseline characteristics of both pre- and post-PSM patients were summarized in Table 1. Before PSM, significant differences were detected in all the demographic and clinical characteristics between patients with AA and ASCC ($p < 0.05$). Compared with patients with ASCC, AA patients were more commonly happened in male and elder population (> 70 years old) and had a higher tendency to be well differentiated. ASCC was more likely to occur in unmarried population. Notably, patients with AA were prone to metastasize, including the occurrence of bone, liver, lung, and brain metastasis. To better understand the characteristics of tumor metastasis in the patients with AA and ASCC, we analyzed four common metastatic organs (brain, liver, bone, and lung metastasis) by Venn diagram. Liver and lung are the most common organ of metastasis for both AA and ASCC. The proportion of synchronous two metastatic organ in AA was higher than ASCC (26.2% vs 17.7%), while the proportion of isolated metastatic lesion in AA was lower than ASCC (70.6% vs 79.1%) (Supplementary Fig. 2). As regarding to treatment, more patients with AA underwent surgery, while fewer received radiation and chemotherapy as compared with patients with ASCC. Almost all the variables were well-balanced after PSM, other than race, and liver metastasis (Table. 1).

Table 1
Baseline characteristics of whole cohort before and after 1:1 PSM

Characteristics	Data before PSM			Data after PSM		
	AA	ASCC	p	AA	ASCC	p
	n = 749	n = 7152		n = 747	n = 747	
Age			< 0.001			0.432
Age ≤ 50	105(14.0)	1,439(20.1)		105(14.1)	99(13.3)	
Age 50–70	349(46.6)	4,266(59.6)		349(46.7)	374(50.1)	
Age > 70	295(39.4)	1,447(20.2)		293(39.2)	274(36.7)	
Sex			< 0.001			0.277
Male	384(51.3)	2,482(34.7)		383(51.3)	361(48.3)	
Female	365(48.7)	4,670(65.3)		364(48.7)	386(51.7)	
Race			< 0.001			< 0.001
White	569(76.0)	6,101(85.3)		567(75.9)	581(77.8)	
Black	107(14.3)	805(11.3)		107(14.3)	107(14.3)	
Other	69(9.2)	184(2.6)		69(9.2)	38(5.1)	
Unknown	4(0.5)	62(0.9)		4(0.5)	21(2.8)	
Marital status			< 0.001			0.238
Married	565(75.4)	4,592(64.2)		564(75.5)	550(73.6)	
Unmarried	124(16.6)	2,066(28.9)		123(16.5)	146(19.5)	
Unknown	60(8.0)	494(6.9)		60(8.0)	51(6.8)	
Grade			< 0.001			0.120
I-II	463(61.8)	3,068(42.9)		461(61.7)	458(61.3)	
III-IV	124(16.6)	2,019(28.2)		124(16.6)	150(20.1)	
Unknown	162(21.6)	2,065(28.9)		162(21.7)	139(18.6)	
T			< 0.001			0.362
T1-2	345(46.1)	4,045(56.6)		345(46.2)	350(46.9)	
T3-4	193(25.8)	1,625(22.7)		192(25.7)	170(22.8)	
Unknown	211(28.2)	1,482(20.7)		210(28.1)	227(30.4)	
N			0.049			0.689
0	470(62.8)	4,621(64.6)		468(62.7)	475(63.6)	
1	222(29.6)	2,142(29.9)		222(29.7)	209(28.0)	
Unknown	57(7.6)	389(5.4)		57(7.6)	63(8.4)	
M			< 0.001			0.054
0	604(80.6)	6,468(90.4)		604(80.9)	624(83.5)	
1	111(14.8)	461(6.4)		109(14.6)	80(10.7)	
Unknown	34(4.5)	223(3.1)		34(4.6)	43(5.8)	
Bone metastasis			0.019			0.132
No	706(94.3)	6,886(96.3)		704(94.2)	711(95.2)	
Yes	12(1.6)	62(0.9)		12(1.6)	4(0.5)	
Unknown	31(4.1)	204(2.9)		31(4.1)	32(4.3)	

Abbreviations: AA anal canal adenocarcinomas; **ASCC** squamous cell carcinoma of the anal; **NOS** No other specific; **T** Tumor; **N** Lymph node; **M** Metastasis; **Grade I** = Well differentiated; **II** = Moderately differentiated; **III** = Poorly differentiated; **IV** = Undifferentiated

Characteristics	Data before PSM			Data after PSM		
	AA	ASCC	p	AA	ASCC	p
	n = 749	n = 7152		n = 747	n = 747	
Brain metastasis			< 0.001			0.134
No	714(95.3)	6,949(97.2)		713 (95.4)	716 (95.9)	
Yes	4(0.5)	1(0.0)		4 (0.5)	0 (0.0)	
Unknown	31(4.1)	202(2.8)		30 (4.0)	31 (4.1)	
Liver metastasis			< 0.001			0.038
No	665(88.8)	6,742(94.3)		664(88.9)	682(91.3)	
Yes	52(6.9)	203(2.8)		51(6.8)	29(3.9)	
Unknown	32(4.3)	207(2.9)		32(4.3)	36(4.8)	
Lung metastasis			< 0.001			0.092
No	660(88.1)	6,851(95.8)		660(88.4)	673(90.1)	
Yes	54(7.2)	91(1.3)		53(7.1)	34(4.6)	
Unknown	35(4.7)	210(2.9)		34(4.6)	40(5.4)	
Surgery			< 0.001			0.359
No	277(37.0)	4,401(61.5)		276(36.9)	258(34.5)	
Yes	472(63.0)	2,751(38.5)		471(63.1)	489(65.5)	
Radiation			< 0.001			1.000
No/Unknown	328(43.8)	1,339(18.7)		326(43.6)	327(43.8)	
Yes	421(56.2)	5,813(81.3)		421(56.4)	420(56.2)	
Chemotherapy			< 0.001			0.875
No/Unknown	309(41.3)	1,538(21.5)		309(41.4)	313(41.9)	
Yes	440(58.7)	5,614(78.5)		438(58.6)	434(58.1)	

Abbreviations: AA anal canal adenocarcinomas; **ASCC** squamous cell carcinoma of the anal; **NOS** No other specific; **T** Tumor; **N** Lymph node; **M** Metastasis; **Grade I** = Well differentiated; **II** = Moderately differentiated; **III** = Poorly differentiated; **IV** = Undifferentiated

Univariate and multivariate analysis

For the whole cohort prior to match, the following variables i.e., age, sex, race, marital status, grade, T, N, M stage, bone, liver, brain, lung metastasis, chemotherapy, radiotherapy, and surgery were independent prognostic factors. And those variables were further used for matching (Supplementary Table 1). In order to identify potential predictors of CSS in AA cohort, univariate and multivariate analyses were performed (Table.2). In univariate analysis, the following factors, including age, grade, T stage, N stage, M stage, and surgery were associated with CSS ($p < 0.05$). The above variables were incorporated into multivariate analysis. Based on multivariate analysis, variables like age, grade, T stage, N stage, M stage, surgery, and chemotherapy were identified as independent predictors of patients with AA. Surgical treatment, and administration of chemotherapy were positively associated with survival of AA. Conversely, age, worse grade, advanced T, N stage, and organ metastasis were negatively associated with survival in patients with AA. As for patients with ASCC, female, surgery, and administration of radiation or chemotherapy were all significantly positively associated with prognosis. However, older age (> 70-year-old), black race, unmarried status, poor grade, higher T, N stage, and the presence of metastasis were negatively associated with survival (Table. 2).

Table 2
Univariate and multivariate analysis of CSS in patients with AA/ASCC prior to match

Variates	AA						ASCC					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95.0% CI	p	HR	95.0% CI	p	HR	95.0% CI	p	HR	95.0% CI	p
Age												
Age ≤ 50	Reference			Reference			Reference			Reference		
Age 50–70	0.730	0.495–1.077	0.113	0.869	0.581–1.301	0.496	1.035	0.890–1.203	0.657	1.146	0.980–1.339	0.087
Age > 70	1.445	1.003–2.110	0.048	1.931	1.297–2.877	0.001	1.889	1.599–2.231	< 0.001	2.125	1.777–2.542	< 0.001
Sex												
Male	Reference						Reference			Reference		
Female	0.907	0.706–1.165	0.445				0.657	0.588–0.735	< 0.001	0.632	0.561–0.712	< 0.001
Race												
White	Reference						Reference			Reference		
Black	0.936	0.647–1.356	0.728				1.405	1.202–1.642	< 0.001	1.300	1.104–1.532	0.002
Other	1.251	0.830–1.887	0.284				1.298	0.943–1.787	0.110	1.166	0.846–1.608	0.348
Unknown	0.624	0.087–4.459	0.638				0.272	0.088–0.845	0.024	0.251	0.081–0.783	0.017
Marital status												
Married	Reference						Reference			Reference		
Unmarried	1.217	0.875–1.692	0.244				1.248	1.140–1.446	< 0.001	1.157	1.015–1.320	0.029
Unknown	1.024	0.658–1.595	0.915				0.889	0.699–1.131	0.338	0.764	0.597–0.979	0.033
Grade												
I-II	Reference			Reference			Reference			Reference		
III-IV	1.864	1.367–2.543	< 0.001	1.686	1.218–2.333	0.002	1.226	1.077–1.396	0.002	1.165	1.020–1.331	0.024
Unknown	1.267	0.926–1.735	0.139	0.995	0.724–1.367	0.975	0.939	0.818–1.078	0.374	0.875	0.761–1.006	0.060
T												
T1-2	Reference			Reference			Reference			Reference		
T3-4	2.334	1.680–3.243	< 0.001	1.505	1.056–2.145	0.024	2.963	2.606–3.369	< 0.001	2.265	1.977–2.596	< 0.001
Unknown	3.224	2.372–4.382	< 0.001	1.878	1.334–2.643	< 0.001	2.043	1.772–2.356	< 0.001	1.573	1.350–1.834	< 0.001
N												
0	Reference			Reference			Reference			Reference		
1	2.196	1.678–2.874	< 0.001	1.817	1.332–2.479	< 0.001	2.228	1.985-2.500	< 0.001	1.654	1.451–1.887	< 0.001
Unknown	3.086	2.075–4.591	< 0.001	1.330	0.796–2.223	0.276	2.120	1.709–2.630	< 0.001	1.264	0.950–1.683	0.108
M												
0	Reference			Reference			Reference			Reference		

Variates	AA						ASCC					
1	5.302	4.020–6.993	< 0.001	3.513	2.547–4.846	< 0.001	5.901	5.140–6.775	< 0.001	3.948	3.396–4.589	< 0.001
Unknown	2.544	1.540–4.205	< 0.001	0.863	0.448–1.663	0.660	1.832	1.392–2.410	< 0.001	1.051	0.728–1.517	0.791
Surgery												
No	Reference			Reference			Reference			Reference		
Yes	0.225	0.173–0.291	< 0.001	0.331	0.246–0.445	< 0.001	0.595	0.527–0.672	< 0.001	0.639	0.560–0.730	< 0.001
Radiotherapy												
No/Unknown	Reference			Reference			Reference			Reference		
Yes	0.840	0.653–1.079	0.172	1.155	0.821–1.624	0.409	0.597	0526-0.678	< 0.001	0.775	0.649–0.926	0.005
Chemotherapy												
No/Unknown	Reference			Reference			Reference			Reference		
Yes	0.839	0.652–1.080	0.172	0.577	0.415–0.803	0.001	0.640	0.566–0.725	< 0.001	0.556	0.466–0.662	< 0.001

Abbreviations: AA anal canal adenocarcinomas; **ASCC** squamous cell carcinoma of the anal; **NOS** No other specific; **T** Tumor; **N** Lymph node; **M** Metastasis; **OS** Overall survival; **HR**: Hazard ratio; **CI**: Confidence interval. **Grade I**=Well differentiated; **II**=Moderately differentiated; **III**=Poorly differentiated; **IV**=Undifferentiated
Note: Other include American Indian/Alaskan native, and Asian/Pacific Islander, and others unspecified.

Survival analysis

Before PSM, AA was associated with unfavorable CSS ($p < 0.001$) and OS ($p < 0.001$) compared with ASCC. The 1- ,3- and 5-year CSS rate of AA and ASCC were 86.0%, 64.8%, 56.9% and 92.3%, 81.5%, 77.9%, respectively. And the 1- ,3- and 5-year OS rate of AA and ASCC were 81.9%, 57.2%, 45.8% and 89.3%, 74.0%, 65.9%, respectively. However, after PSM, patients with AA were associated with a longer OS than those with ASCC (48.0 vs. 35.0 months, $p < 0.001$), while there is no significant difference in CSS ($p = 0.140$). The 1- ,3- and 5-year CSS rate of AA and ASCC were 86.1%, 65.1%, 57.1% and 80.2%, %, 62.5%, 56.1%, respectively (Fig. 1).

We conducted a stratification analysis to further evaluate the prognostic variables in patients with AA. Survival beneficial factors could be achieved in patients with AA, including the age (range from 50 to 70 years old), absence of N stage or organ metastasis, surgery, and chemotherapy. Notably, patients with AA were associated with a longer survival regardless of the state of T stage (Fig. 2).

Nomogram establishment and assessment in patients with AA

To further eliminate confounding factors, the unknown variables were excluded and a total of 400 AA patients without unknown variables derived from SEER database were used to establish the nomogram prediction model and applied as internal validation (Supplementary Fig. 1.). The univariate and multivariate Cox analysis was performed to filter all factors to establish the nomogram in patients with AA based on the SEER database (Supplementary Table 2). The age, sex, grade, M stage, and surgery were independent prognostic factors of CSS. And these factors were included in the mode.

112 patients from WCH database were used as external validation. The demographic and clinical characteristics of external validation were shown in Supplementary Table.3. The predictive model was demonstrated in the form of a novel nomogram (Fig. 3). The novel model was validated by C-index, calibration curves and DCA. The C-index of the nomogram was 0.78 and 0.735 in internal and external validation, respectively, which suggested the good discrimination power of the model. By bootstrap sampling for 1000 times, calibration curves of this nomogram were plotted (Fig. 3) and suggested good concordance between the predicted and actual probabilities. Furthermore, DCA of SEER training set showed a great positive net benefits in the predictive model among almost all the threshold probabilities at 1-, 3-, and 5-year, indicating the favorable potential clinical effect of the predictive model. Similarly, DCA of real-world validation set also revealed a positive net benefit in the predictive model among almost all the threshold probabilities at 1-, 3-, and 5-year (Fig. 4).

Risk Classification System

Based on the novel model, a risk classification system for CSS was established. All patients in the training and validation group were divided into low-risk, intermediate-risk group, and high-risk prognostic cohorts, with trisection score values 70.5 and 146.3 in internal validation group and 70.5 and 146.3 in external validation group, respectively. The Kaplan-Meier curves of three risk classification groups suggested that CSS in the different cohorts was well differentiated by the risk classification system. The low-risk prognostic cohort showed significant survival advantages compared with

intermediate-risk and high-risk group ($p < 0.001$) in both training and validation cohort. Similarly, intermediate-risk cohort was associated with significantly improved survival in contrast to high-risk cohort ($p < 0.001$) (Supplementary Fig. 3).

Discussion

AA is a rare malignancy, accounting for only 1% of gastrointestinal neoplasms[1] and the understanding of AA remained limited. In our study, we applied a PSM to analyze the demographic and clinical differences between AA and ASCC. Elder population (> 70 years old), better differentiation, and metastasis were more common in patients with AA. Before-PSM, AA has worser CSS and OS compared to ASCC. Conversely, after PSM, patients with AA had a longer OS than those with ASCC, especially in subpopulation who had age range from 50 to 70 years old, were absence of organ metastasis, underwent surgery or chemotherapy. The age, sex, grade, M stage, and surgery were independent prognostic factor of CSS in patients with AA and were included in establishing nomogram, which showed excellent accuracy and efficiency in prediction of CSS in AA patients.

It is controversial of the prognosis for adenocarcinoma (AC) and SCC. The current studies revealed diverse conclusions in survival advantages between AC and SCC in different locations[13–15]. As regarding to anal canal, previous studies indicated that AA has a worser prognosis compared with ASCC[3, 4, 16, 17]. Robert A Franklin et.al., revealed that the lack of a standard approach to the treatment of AA might be associated with the poor prognosis[3]. Another retrospective study[7] suggested that AA patients were more likely to occur in older age, advanced stage, which may result in the poor prognosis of AA. In our study, AA was associated with a worser survival before PSM. Compared with ASCC, AA was inclined to occur in advanced T stage, older age, and have a higher proportion of metastases. Besides, a lower proportion of patients with AA suffered from the chemotherapy and radiation. It appears that these aggressive factors may contribute to its worse survival. In order to make the above uneven variables well-balanced and comparable, a PSM was established to analyze the prognostic distinguish between AA and ASCC. And survival analysis was also performed after PSM. The results indicated that AA has a similar CSS to ASCC and was associated with a significantly prolonged OS compared to ASCC, which shows that AA has a better prognosis under the same baseline variables. It remained unclear about the concreate mechanism of well prognosis of AA. It was difficult to identify whether prognosis was associated with pathologic difference. Patients with AA was related to worse survival compared with those with rectal adenocarcinoma [3], indicating that histology alone cannot explain the survival difference between AA and ASCC. Further large-scale studies are needed to explore the potential molecular mechanism.

Due to the rarity of AA, no standard treatment guidelines exist currently. Therapeutic regimens of AA were derived from the rectal adenocarcinoma treatment, with frequent use of neoadjuvant chemoradiation followed by transabdominal resection[17–19]. A retrospective study based on National Cancer Database reported that surgery in the initial management could improve survival compared to chemoradiation alone and should be considered as internal part of the management of AA[18]. Other studies also concluded the crucial role of surgery in treatment of AA[20, 21]. While another study explored that chemoradiation prolonged survival compared to the radiotherapy plus surgery therapy as well as surgery alone, and it recommended surgery as salvage treatment. But this study only reported 6 of 88 patients who were treated with surgery alone, which made the comparison lacking of rationality[22]. In the largest series of AA to date, chemoradiation followed by surgical resection was associated with a significant improved survival compared with chemoradiation alone after PSM[23]. In our study, surgery and chemotherapy were independent prognostic factors of survival of AA. In a word, surgical resection combined with chemotherapy or radiation may offer the best chance of survival in patients with AA.

In our study, a novel nomogram was established and suggested that age, sex, grade, surgery, and M stage were independent factors of prognosis of AA, and the conclusion was further verified by C-index, DCA, and calibration curves. There are also studies investigating the prognostic factors in patients with AA. Gary D Lewis et al.[7] conducted a retrospective study of 1183 patients from the National Cancer Data Base (NCDB) to evaluate the prognostic risk factors of AA. They found the following factors like older age, male gender, T stage of 3 or higher, more comorbidity, and lower income were associated with worse survival. In the study conducted by QH Wang, the number of positive lymph nodes was an independent prognostic factor of AA[6]. Other variables, including T and N stage, histologic grade, and treatment modality also have impact on the survival of AA[22]. However, those studies did not establish a predictable model to identify prognostic factors of AA. For the first time, we performed a novel nomogram of AA and the nomogram was validated in different ways, which is more precise to predict the prognosis of patients with AA.

Though we successfully constructed and validated a nomogram to predict individual survival probability for patients with AA, our study did have several limitations. First, some important factors may be overlooked due to unavailable data in the SEER database, such as chemotherapy regimen, targeted therapy. Second, single-center data were used for external validation. Although the model still worked well, multi-institutional external validation would provide more convincing evidence. To avoid these limitations, some large prospective randomized controlled trials are wanted in the future.

Conclusion

In summary, there were significant differences between AA and ASCC ranging from baseline characteristics to survival traits. Patients with AA have a worser prognosis compared with those with ASCC before-PSM. While through balancing the baseline characteristic, we discovered that patients with AA were related to a better OS than those with ASCC. A novel nomogram was established to predict the CSS of AA patients. C-index, DCA, calibration curves as well as stratified analysis were used to validate the model, which was proved has accurate predicting ability. The nomogram would be helpful for clinicians to evaluate the individual survival of AA patients accurately and identify high-risk patients who need more aggressive treatment and follow-up strategies.

Declarations

Conflict of interest disclosure

All authors declared no conflict of interest.

Acknowledgements

The authors thank all clinicians in Department of Cancer Center, West China Hospital, Sichuan University, for available database on all patients in this study.

Authors contribution

Yu-Wen Zhou and Gui-Xia Wei wrote the main manuscript text. Lian-Sha Tanga and Jia-Ling Wanga prepared all the figures and tables. And Meng Qiu reviewed the manuscript.

Funding support

This work was supported by 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC21017)

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. 2018;68(1):7-30.
2. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol. 2014;40(10):1165-76.
3. Franklin RA, Giri S, Valasareddy P, Lands LT, Martin MG. Comparative Survival of Patients With Anal Adenocarcinoma, Squamous Cell Carcinoma of the Anus, and Rectal Adenocarcinoma. Clin Colorectal Cancer. 2016;15(1):47-53.
4. Anwar S, Welbourn H, Hill J, Sebag-Montefiore D. Adenocarcinoma of the anal canal - a systematic review. Colorectal Dis. 2013;15(12):1481-8.
5. Liu J, Huang X, Yang W, Li C, Li Z, Zhang C, et al. Nomogram for predicting overall survival in stage II-III colorectal cancer. Cancer Med. 2020;9(7):2363-71.
6. Wang Q, Fu J, Chen X, Cai C, Ruan H, Du J. What factors are associated with the poor prognosis of anal adenocarcinoma compared with low-lying rectal adenocarcinoma based on a population analysis: A propensity score matching study. PLoS One. 2019;14(7):e0219937.
7. Lewis GD, Haque W, Butler EB, Teh BS. Survival Outcomes and Patterns of Management for Anal Adenocarcinoma. Ann Surg Oncol. 2019;26(5):1351-7.
8. Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol. 2011;29(23):3163-72.
9. Han DS, Suh YS, Kong SH, Lee HJ, Choi Y, Aikou S, et al. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. J Clin Oncol. 2012;30(31):3834-40.
10. Sternberg CN. Are nomograms better than currently available stage groupings for bladder cancer? J Clin Oncol. 2006;24(24):3819-20.
11. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31(9):1188-95.
12. Ersek JL, Symanowski JT, Han Y, Howard A, Dumas K, Ahrens W, et al. Pulmonary Carcinosarcoma: A Surveillance, Epidemiology, and End Results (SEER) Analysis. Clin Lung Cancer. 2020;21(2):160-70.
13. Wang BY, Huang JY, Chen HC, Lin CH, Lin SH, Hung WH, et al. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. J Cancer Res Clin Oncol. 2020;146(1):43-52.
14. Makarova-Rusher OV, Ulahannan S, Greten TF, Duffy A. Pancreatic Squamous Cell Carcinoma: A Population-Based Study of Epidemiology, Clinicopathologic Characteristics and Outcomes. Pancreas. 2016;45(10):1432-7.
15. Pan X, Yang W, Wen Z, Li F, Tong L, Tang W. Does adenocarcinoma have a worse prognosis than squamous cell carcinoma in patients with cervical cancer? A real-world study with a propensity score matching analysis. J Gynecol Oncol. 2020;31(6):e80.
16. Tsay CJ, Pointer T, Chandler JB, Nagar AB, Protiva P. Anal adenocarcinoma: case report, literature review and comparative survival analysis. BMJ Open Gastroenterol. 2021;8(1).
17. Malakhov N, Kavi AM, Lee A, Adedoyin P, Sheth N, Lederman AJ, et al. Patterns of Care and Comparison of Outcomes Between Primary Anal Squamous Cell Carcinoma and Anal Adenocarcinoma. Dis Colon Rectum. 2019;62(12):1448-57.
18. Wegner RE, White RJ, Hasan S, Raj M, Monga D, Finley G, et al. Anal adenocarcinoma: Treatment outcomes and trends in a rare disease entity. Cancer Med. 2019;8(8):3855-63.

19. Basik M, Rodriguez-Bigas MA, Penetrante R, Petrelli NJ. Prognosis and recurrence patterns of anal adenocarcinoma. Am J Surg. 1995;169(2):233-7.
20. Kounalakis N, Artinyan A, Smith D, Mojica-Manoso P, Paz B, Lai LL. Abdominal perineal resection improves survival for nonmetastatic adenocarcinoma of the anal canal. Ann Surg Oncol. 2009;16(5):1310-5.
21. Chang GJ, Gonzalez RJ, Skibber JM, Eng C, Das P, Rodriguez-Bigas MA. A twenty-year experience with adenocarcinoma of the anal canal. Dis Colon Rectum. 2009;52(8):1375-80.
22. Belkacémi Y, Berger C, Poortmans P, Piel G, Zouhair A, Méric JB, et al. Management of primary anal canal adenocarcinoma: a large retrospective study from the Rare Cancer Network. Int J Radiat Oncol Biol Phys. 2003;56(5):1274-83.
23. Li R, Shinde A, Fakih M, Sentovich S, Melstrom K, Nelson R, et al. Impact of Surgical Resection on Survival Outcomes After Chemoradiotherapy in Anal Adenocarcinoma. J Natl Compr Canc Netw. 2019;17(10):1203-10.

Figures

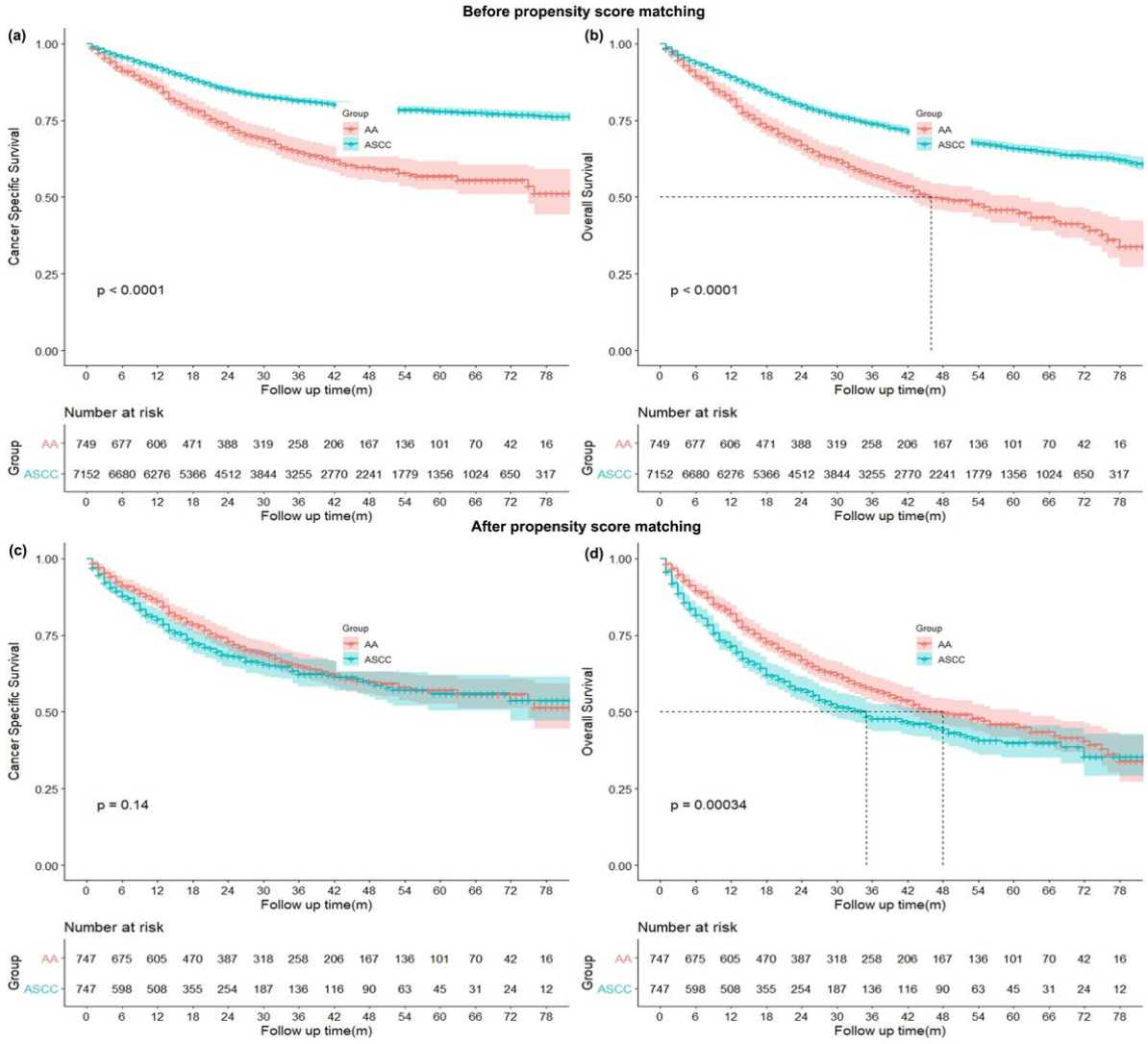

Figure 1

Survival curves prior to match and matched cohorts: (a) CSS and (b) OS of unmatched cohort; (c) CSS and (d) OS of matched cohort.

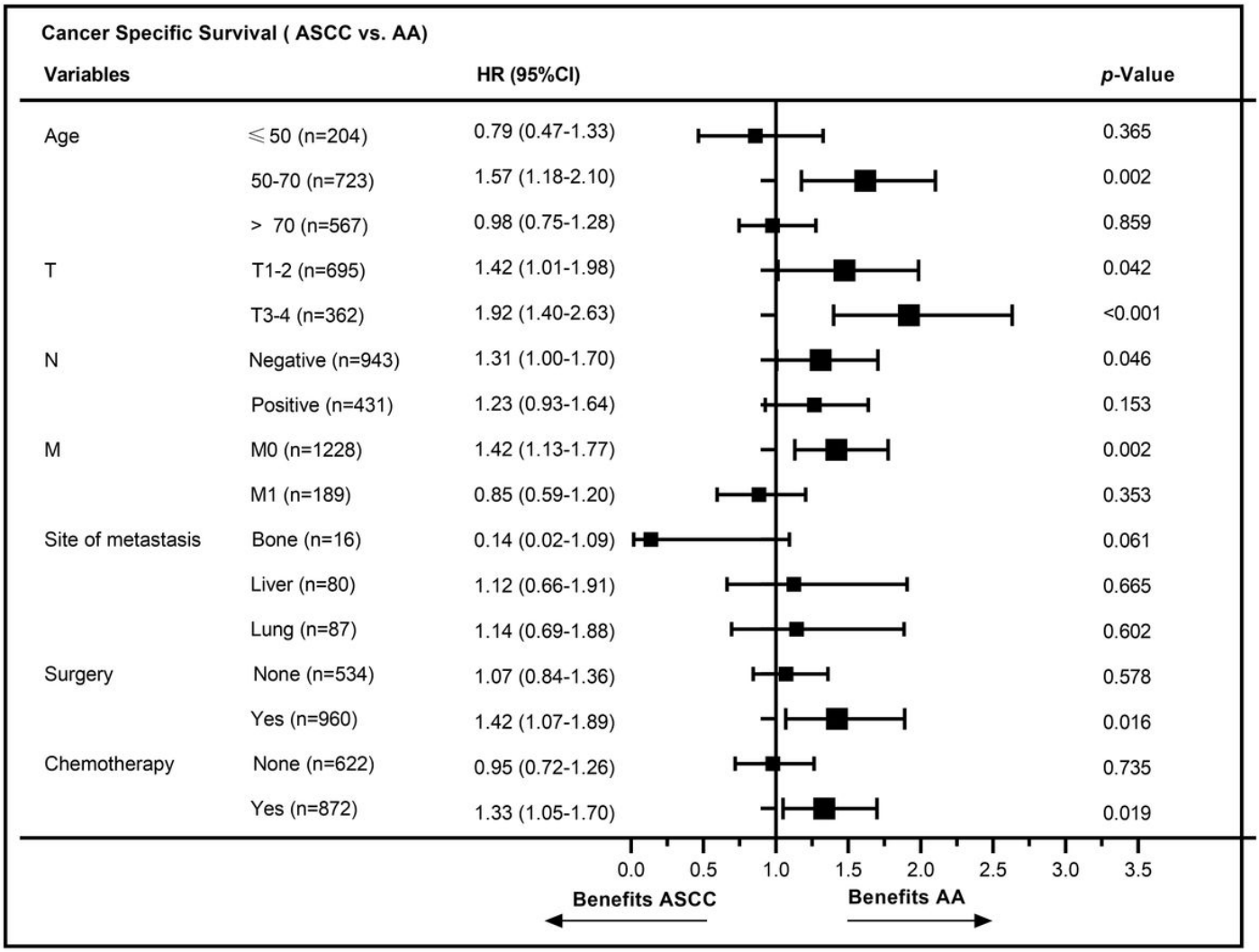

Figure 2

Stratified analysis between anal canal adenocarcinomas (AA) and anal canal squamous cell carcinomas (ASCC) in matched cohorts.

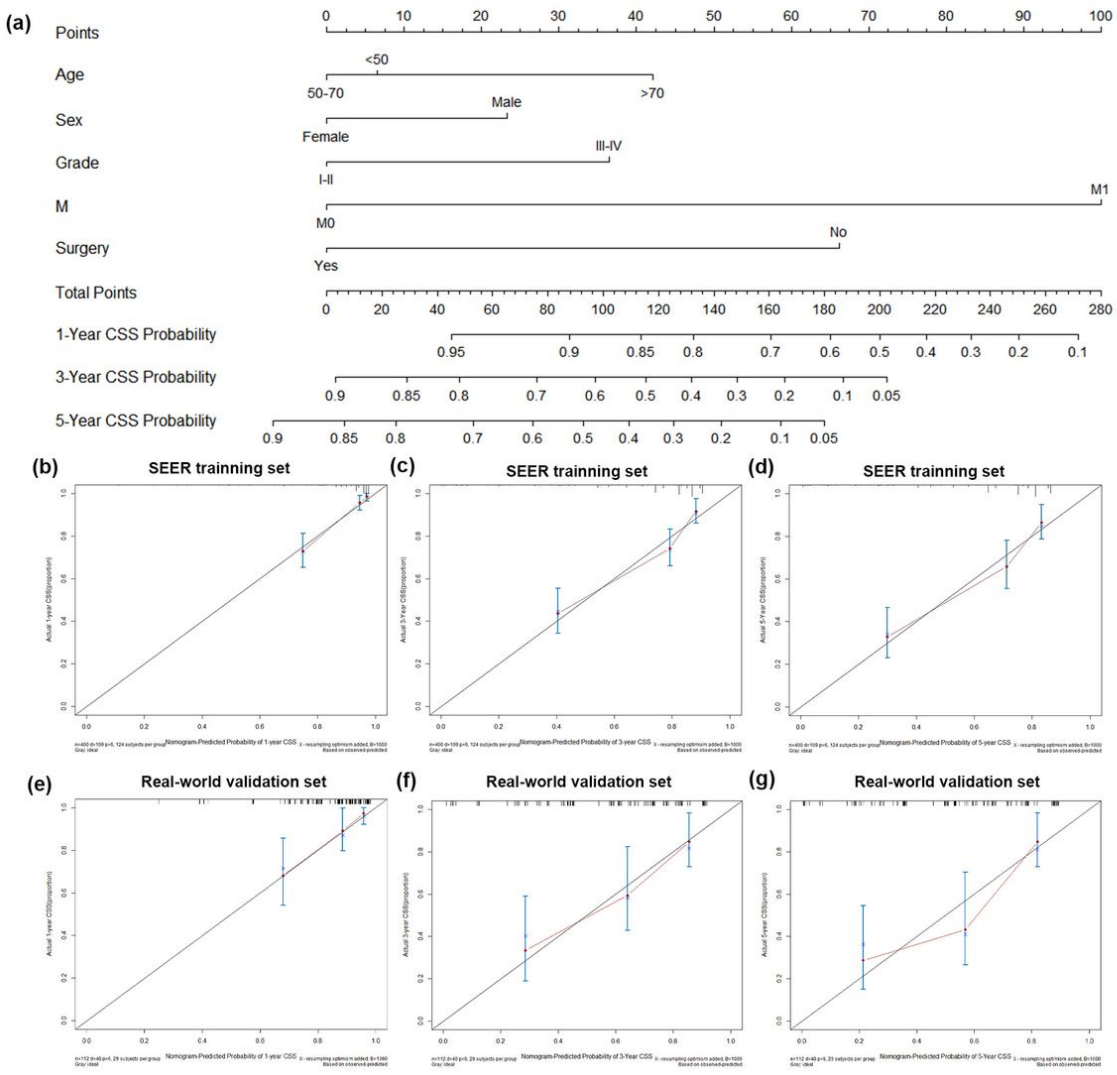

Figure 3

(a). A novel nomogram to predict the CSS of patients with AA; The calibration curves for predicting the probability of 1-, 3-, 5-year CSS in internal validation (b-d) and external validation (e-g). The figures showed a good consistency in the probability of 1-, 3-, and 5-year CSS either internal or external validation.

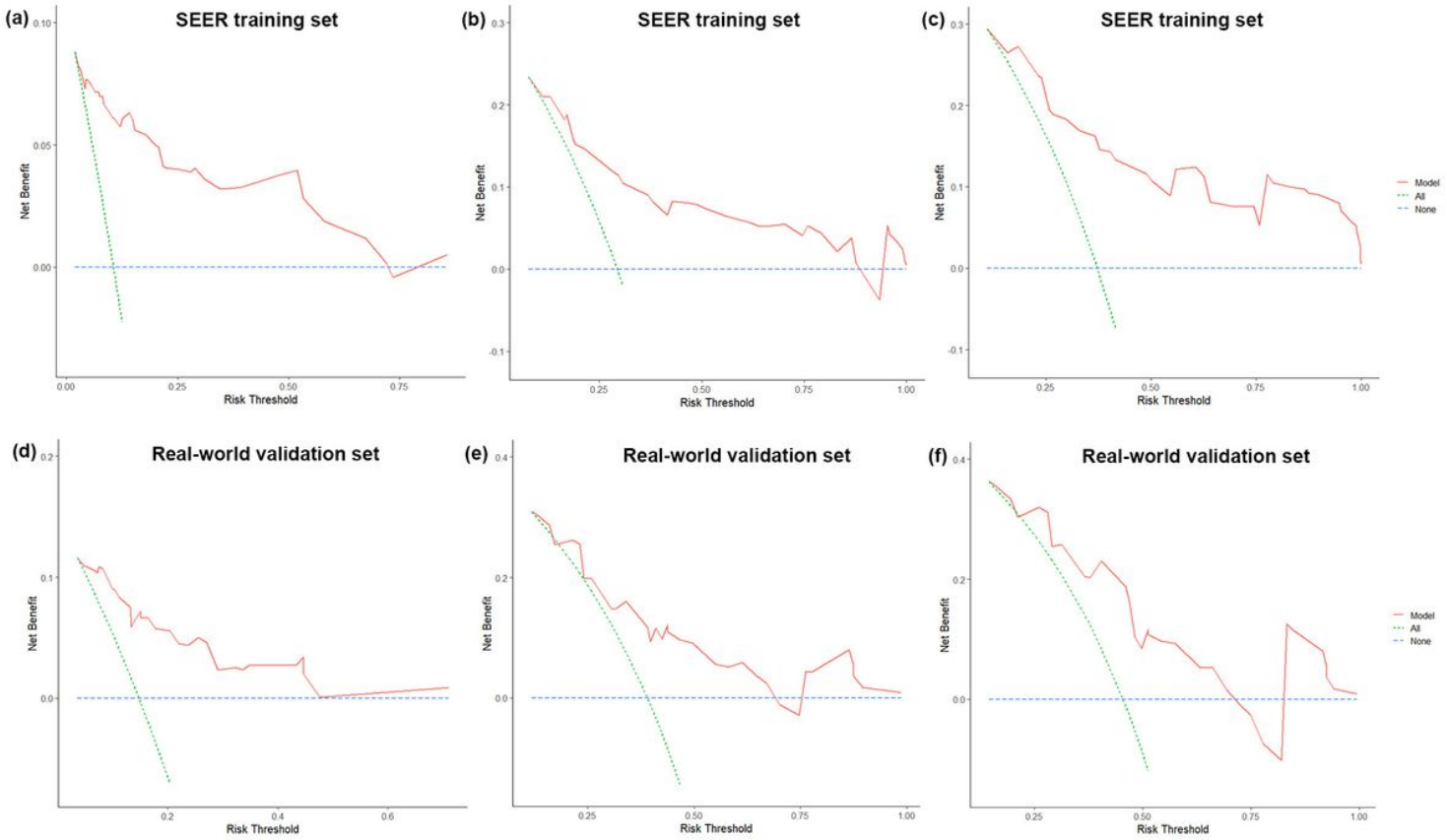

Figure 4

DCA for the nomogram in prediction of prognosis of patients with AA at 1-, 3-, and 5-year point in the training cohort (a-c) and in the validation cohort (d-f). The plots demonstrated great positive net benefits in the predictive model among almost all threshold probabilities at 1-, 3-, and 5-year.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFig.1..jpg
- SupplementaryFig.2..jpg
- SupplementaryFig.3..jpg
- SupplementaryTable1.docx
- SupplementaryTable2.docx
- SupplementaryTable3.docx