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ORIGINAL ARTICLE – COLORECTAL CANCER

Risk Stratification in Patients with Stage II Colon Cancer

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ABSTRACT

Background. The decision to receive adjuvant chemotherapy is far from evident and remains controversial in patients with American Joint Committee on Cancer stage II colon cancer. This study analyzes several pathological characteristics in order to assess their (combined) predictive value for outcomes in stage II colon cancer.

Methods. All stage II patients treated surgically for colon cancer at our tertiary care center (2004–2011) were extracted from a prospectively maintained, Institutional Review Board-approved data repository (n = 313). Mortality and metastasis were compared, including multivariable Cox regression adjusted for stage subdivisions (IIA/IIB/IIC) and potential confounders.

Results. Colon cancer-specific mortality was substage independently increased in patients with baseline carcinoembryonic antigen (CEA) >5 ng/L [hazard ratio (HR) 2.88; $p = 0.022$], large vessel invasion (LVI; HR 4.59; $p < 0.001$), perineural invasion (HR 3.08; $p = 0.006$), and extramural vascular invasion (EMVI; HR 4.96; $p < 0.001$). Overall mortality adjusted for substage, age, and comorbidity was also significantly higher in patients with high-grade disease (HR 2.54; $p < 0.001$), LVI (HR 1.74; $p = 0.015$), perineural (HR 2.42; $p < 0.001$), and EMVI (HR 2.79; $p < 0.001$). Metastatic recurrence adjusted for adjuvant chemotherapy status had substage-independent associations with baseline CEA >5 ng/L (HR 2.37; $p = 0.046$), LVI (HR 3.07; $p = 0.001$), perineural invasion (HR 2.57; $p = 0.010$), and EMVI (HR 2.83; $p = 0.002$). The number of high-risk features (0, 1, 2–3, 4+) was associated with a clear incremental increase in overall and disease-specific mortality and recurrence ($p \leq 0.001$). The major inflection point is at two high-risk characteristics or more, whereas 5-year survival is almost halved from 77.4 % to 31.7 % ($p < 0.001$).

Conclusions. The risk score introduced provides a prognostic tool based on readily available data extracted from baseline pathology and preoperative CEA, which provides an easy method to stratify risks of mortality and recurrence and may therefore help in treatment decisions after surgery in stage II patients.

Colonic adenocarcinoma invading beyond the muscularis propria of the colon wall without lymph node involvement or distant metastasis is defined by the American Joint Committee on Cancer (AJCC) as stage II.[1] Patients with stage II disease form a very heterogeneous group in terms of risks or recurrence and subsequent outcomes.[2] In an effort to further stratify these risks, tumors were subdivided by T stage within the 6th edition of the AJCC staging manual,[3] introducing stage IIA (T-stage 3 tumors invading through the muscularis propria and into pericolic tissues) and stage IIB for T4 tumors. The 7th edition further subdivided T-stage 4 tumors into stage IIB (T4a: tumor penetrating to the surface of the visceral peritoneum) and stage IIC (T4b stage: tumor directly invading or adherent to other organs or structures), the latter being a considerably higher-risk form. Despite these incremental subdivisions, AJCC stage II colon cancer patients still form a mixed group where outcomes vary from being close to stage I tumors in recurrence and survival to being worse than many node-positive cases.[4]

Therefore, the choice to either undergo or forego adjuvant chemotherapy is far from evident and subject to risks of both overtreatment and undertreatment. Separate high- and low-risk profiles for stage II colon cancer using

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secondary pathologic characteristics, including tumor grade, lymph node yield, and resection margins, were introduced by the American Society for Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) in order to facilitate decision making.[5,6] However, large-scale studies evaluating treatment adherence to stage-specific recommendations[6] based on this risk stratification show that in nearly half of all cases, these guidelines are not followed,[7] and the explanations for this remain largely speculative. However, this signals that current risk-based recommendations do not adequately reflect clinicians' assessments in practice, which may call for the development of additional tools to adequately estimate risks and therefore utility of adjuvant treatment.

This study introduces and assesses the prognostic utility of a novel risk estimator that stratifies stage II patients into incremental risk levels using a compounded score based on the presence of five readily available surgical pathological characteristics. We examine the predictive value of these characteristics individually, as wells as in a combined risk score.

METHODS

Patients

All colon cancer patients treated surgically at the Massachusetts General Hospital from 2004 through 2011 (n = 1071) were retrospectively included in a prospectively maintained survival and outcomes database after Institutional Review Board approval. Data on patients were collected from the research patient data repository and the social security death index, as well as patient records from our healthcare network. Due to the significant differences in treatment approach and tumor biology, we exclusively focused on colon cancer and did not include patients with tumors of the rectum. Tumors of the colon were defined as any tumor proximal to the rectosigmoid junction.[8]

Of this cohort, a series of 313 consecutive stage II patients were included for analysis. Mortality, disease-specific mortality and metastasis were compared in these patients, including their relative rates for each of the following five high-risk characteristics: baseline carcinoembryonic antigen (CEA) above 5 ng/L; surgical pathological establishment of high-grade disease, defined in previous work[9] and recommended by the College of American Pathologists (CAP)[10] and the AJCC[1] as tumors with less than 50 % gland formation; extramural vascular invasion (EMVI), defined as the presence of vascular invasion beyond the muscularis propria; large vessel invasion (LVI), defined as tumor present within a blood vessel having a muscular wall, by demonstrating the presence of elastic lamina surrounding a tumor focus on an elastin stain, or both; and, lastly, perineural invasion. All pathological characteristics are demonstrated by representative micrographs in Fig. 1.

Subsequently, these outcomes and the relative hazards of their occurrence were also assessed based on the number of high-risk characteristics present (none, 1, 2–3, 4–5) in order to evaluate the prognostic value of this compounded score that is calculated using the number of high-risk characteristics present.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM SPSS Statistics for Windows; IBM Corporation, Armonk, NY, USA. Release 2013). A two-tailed p value below 0.05 was considered the threshold for statistical significance. Descriptive statistics (percentage, frequency) were used to illustrate the relative distribution of high-risk characteristics over AJCC substage (IIA/IIB/IIC), followed by cross-tabulation of all five high-risk characteristics in order to show overlap, expressed both as percentage rates and Phi correlation coefficients (r_φ). Outcomes analyzed were metastatic recurrence and overall and disease-specific mortality, expressed as percentage outcomes, compared for significance using a Chi-square coefficient, and as the multivariable hazard ratios (HRs) of these outcomes for each high-risk characteristic, after adjustment for adjuvant chemotherapy and AJCC substage for disease-free survival, and AJCC substage, age, adjuvant chemotherapy, and Charlson comorbidity score for survival outcomes. Subsequently, associations between the number of high-risk characteristics (0, 1, 2–3, 4–5) and outcomes were also measured using a Chi-squared test and using a stratified Cox proportional hazards survival model adjusted for AJCC substage and potential confounders.

RESULTS

Patient Characteristics

The stage II patients included consisted mostly of stage IIA patients (75.7 %, 237 of 313), followed by IIB (17.6 %, 55 patients) and IIC (6.7 %, 21 patients). The relative frequency of all five pathologic characteristics in the overall stage II population and for each substage is shown in Table 1. The table also displays a cross-tabulation of these characteristics, which shows how often individual pairs of positive high-risk characteristics were found together. In addition, as a signifier of potential overlap, correlations between the evaluated high-risk characteristics were measured. Apart from the evident link

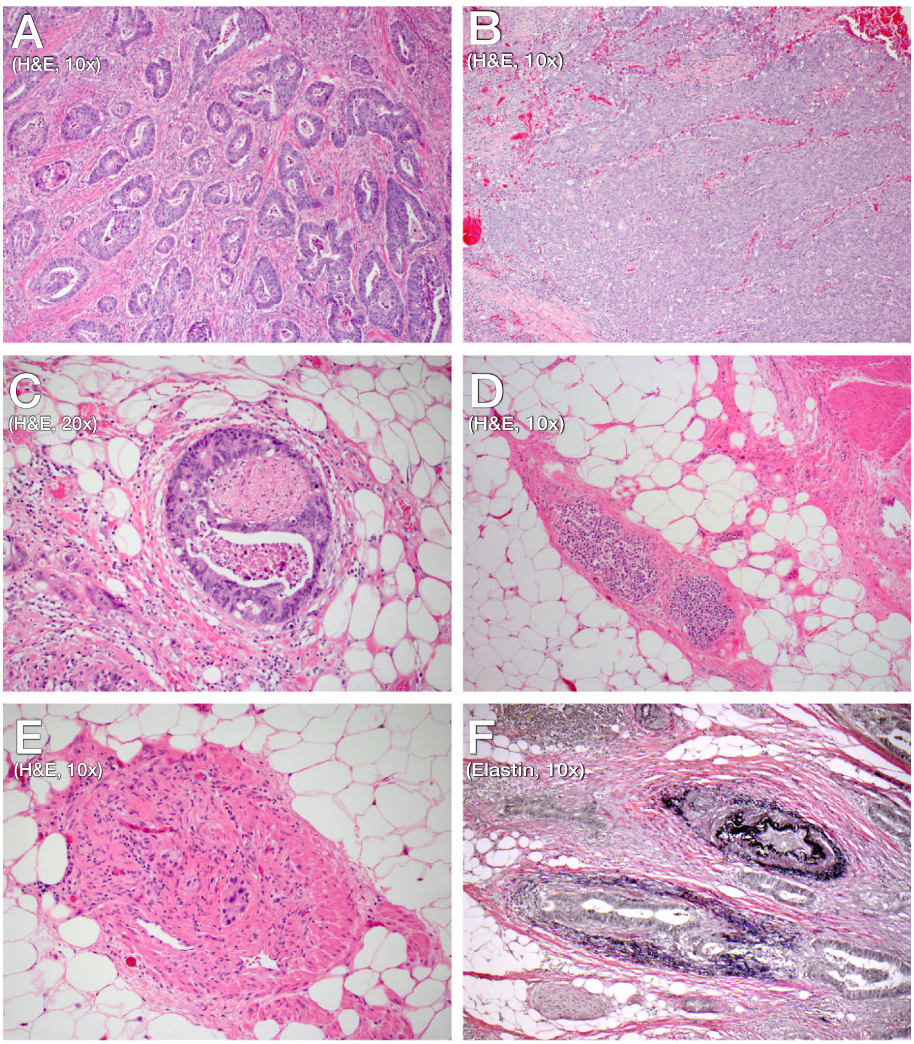

FIG. 1 Representative photomicrographs demonstrating **a** low-grade disease, **b** high-grade disease, **c** perineural invasion, **d** extramural vascular invasion, and **e** large vessel invasion on both H&E and **f** elastin-stained sections. *H&E* hematoxylin and eosin

between EMVI and LVI ($r = 0.59$; $p < 0.001$), the remaining significant correlations encountered were relatively weak correlations between perineural invasion and CEA >5 ng/L ($r = 0.252$; $p < 0.001$), perineural invasion and LVI ($r = 0.162$; $p = 0.005$), high-grade disease and EMVI ($r = 0.152$; $p = 0.007$), and perineural invasion and EMVI ($r = 0.288$; $p < 0.001$).

High-Risk Characteristics and Outcomes

The median duration of follow-up was 64 months (interquartile range 34–85). Table 2 shows the mortality, disease-specific mortality, and recurrence percentages for each high-risk characteristic. Additionally, the added hazards of mortality are also expressed through a multivariable HR in each high-risk category. The association of colon cancer-specific mortality was significantly increased, even after adjustment for AJCC substage, in patients with baseline CEA >5 ng/L (HR 2.88; $p = 0.022$), LVI (HR 4.59; $p < 0.001$), perineural invasion (HR 3.08; $p = 0.006$), and EMVI (HR 4.96; $p < 0.001$). Overall mortality adjusted for substage, age, and comorbidity was also significantly higher in patients with high-grade disease (HR 2.54; $p < 0.001$), large vessel disease (HR 1.74; $p = 0.015$), perineural invasion (HR 2.422; $p < 0.001$), and EMVI (HR 2.79; $p < 0.001$). Metastatic recurrence adjusted for adjuvant chemotherapy status had substage-independent associations with baseline CEA >5 ng/L (HR 2.37; $p = 0.046$), LVI (HR 3.07; $p = 0.001$), perineural invasion (HR 2.57; $p = 0.010$), and EMVI (HR 2.83; $p = 0.002$).

High-Risk Characteristic Strata

An increase in the number of high-risk features was associated with increased chemotherapy use ($p = 0.031$); the vast majority of treatment regimens administered were either FOLFOX, 5-fluorouracil/leucovorin, or Xeloda. The percentage of patients with a lymph node yield of over 12 was not significantly different between risk strata

TABLE 1 Cross-tabulation of pathological characteristics

	All (%) [$n = 313$]	CEA >5 ng/L (%)	High grade (%)	Large vessel (%)	Peri-Neural (%)	EMVI (%)
Stage IIA	75.7	26.9	14.9	19.1	12.8	18.1
	[$n = 237$]	[39/145]		[43/225]	[29/227]	
Stage IIB	17.6	54.5	16.4	40.7	27.3	38.2
	[$n = 55$]	[18/33]		[22/54]	[15/55]	
Stage IIC	6.7	36.5	33.3	15.0	30.0	33.3
	[$n = 21$]	[4/11]		[3/20]	[6/20]	
Baseline CEA >5 ng/L	32.3					
	[61/189]					
High-grade disease	16.4	4.8^{NS}				
		[9/189]				
Large vessel invasion	22.7	8.7^{NS}	3.7^{NS}			
	[68/299]	[16/183]	[11/298]			
Perineural invasion	16.6	9.8***	3.3^{NS}	6.4**		
	[50/302]	[18/184]	[10/300]	[19/298]		
EMVI	22.4	9.5^{NS}	6.1**	15.7***	8.3***	
		[18/189]	[19/311]	[47/299]	[25/302]	

Percentages all based on $n = 313$ unless otherwise specified

CEA carcinoembryonic antigen, *EMVI* extramural vascular invasion

Significance level of correlations between pathologic characteristics with: *NS* not significant, or $p > 0.05$; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

($p = 0.35$), and the number of high-risk features (0, 1, 2–3, 4–5) was associated with a clear incremental increase in overall and disease-specific mortality and recurrence ($p \leq 0.001$). Similar incremental increases were also seen when patients who had not received adjuvant chemotherapy were analyzed separately.

The association between the number of high-risk features and recurrence and mortality was also clearly shown in the multivariable substage-adjusted HRs, which all show at least a doubling of relative hazards for each increment in the number of high-risk features (multivariable HR for disease-specific mortality, 3.4; for metastatic recurrence, 2.59). These same outcomes also had significantly higher hazards per risk score increment for the subset of patients who did not receive adjuvant chemotherapy, with relative hazards also in the 2 or higher range (see Table 3 for details).

Overall, a clear inflection point towards worse outcomes was observed when patients had two or more high-risk characteristics. Figure 2 displays the impact of having two or more high-risk characteristics on survival. The most illustrative figure is the gap in 5-year survival, which is halved from 86.0 % to 41.5 % ($p < 0.001$). In addition, Fig. 2 also visualizes the incremental decrease in survival for every high-risk characteristic increment using a multivariable stratified Cox proportional hazards survival curve adjusted for AJCC substage, age, and comorbidity.

DISCUSSION

Context of the Study

The decision to follow-up surgical resection of stage II colon cancer with adjuvant chemotherapy is a recurring matter of discussion and doubt in clinical practice.[11] This is reflected in population data, where estimates of variations in treatment adherence vary from overtreatment in one-quarter of stage II colon cancer patients considered low risk, to undertreatment in nearly half of all high-risk stage II colon cancer patients.[7] Part of the discrepancy may due to a lack of correlation between the recommendations and the clinicians' assessment, which will more substantially be influenced by patient factors such as age, overall condition, or experience-based physician assessment of the risk of recurrence contrasted by the risks and burden of chemotherapy. Theoretically, the consequences of undertreatment in stage II colon cancer are reflected in distant recurrence, especially since local recurrence is far less common than in rectal tumors.[12] In our population, distant recurrence rates range from 7 % to over 60 % depending on the stage II risk score. On the other hand, overtreatment unnecessarily exposes patients to the potential side effects of chemotherapy, which, in common regimens such as FOLFOX or 5-fluorouracil/leucovorin,

TABLE 2 Associations between outcomes and high-risk characteristics, including multivariable analysis

	Yes (%)	No (%)	HR (95 % CI)	*p* value
Baseline CEA >5 ng/L[a] (incidence: 19.5 %)				
Overall mortality	37.7	21.9	1.71 (0.96–3.06)	0.066
Colon cancer mortality	19.7	6.3	2.88 (1.16–7.11)	0.022
Metastatic recurrence	18.0	8.6	2.37 (1.02–5.50)	0.046
High-grade disease (incidence: 16.3 %)				
Overall mortality	52.9	27.7	2.54 (1.57–4.10)	<0.001
Colon cancer mortality	13.1	8.1	1.92 (0.78–4.70)	0.153
Metastatic recurrence	15.7	11.5	1.62 (0.73–3.56)	0.235
Large vessel invasion (incidence: 21.7 %)				
Overall mortality	42.6	29.0	1.74 (1.11–2.73)	0.015
Colon cancer mortality	20.6	5.6	4.59 (2.14–9.86)	<0.001
Metastatic recurrence	22.1	9.1	3.07 (1.56–6.00)	0.001
Perineural invasion (incidence: 16.0 %)				
Overall mortality	58.0	27.0	2.42 (1.52–3.84)	<0.001
Colon cancer mortality	20.0	7.1	3.08 (1.37–6.91)	0.006
Metastatic recurrence	22.0	10.3	2.57 (1.25–5.29)	0.010
EMVI (incidence: 22.7%)				
Overall mortality	52.1	25.6	2.79 (1.84–4.23)	<0.001
Colon cancer mortality	22.5	5.0	4.96 (2.31–10.7)	<0.001
Metastatic recurrence	23.9	8.7	2.83 (1.46–5.47)	0.002

Overall survival also adjusted for age, Charlson comorbidity score

Metastatic recurrence also adjusted for adjuvant chemotherapy status

HR hazard ratio adjusted for stage II subdivision (stage IIA/IIB/IIC, i.e. T3/T4a/T4b), *CI* confidence interval, *EMVI* extramural vascular invasion, *CEA* carcinoembryonic antigen

[a] Preoperative CEA known in 189/313 patients (60.4 %)

TABLE 3 Outcomes and hazard ratios related to the number of high-risk features

High-risk features	All	0	1	2–3	≥4	*p* value[a]
Number of patients[b]		70	54	50	8	
Lymph node yield >12	89.6	91.4	82.6	86.0	75.0	0.35
Adjuvant chemotherapy (%)	22.5	14.3	20.4	32.0	50.0	0.031
FOLFOX	*55.0*	50.0	54.5	50.0	75.0	–
Xeloda	15.0	40.0	0	12.5	0	–
5-Fluorouracil/leucovorin	22.0	10.0	36.4	18.8	0	–
Other	8.0	0	9.1	18.7	25.0	

High-risk features		0	1	2–3	≥4	*p* value[a]	*m*HR	*p* value
Metastatic recurrence (%)	11.5	7.1	5.6	18.0	50.0	0.001	2.59 (1.72–3.92)	<0.001
Patients without adjuvant chemotherapy	*9.9*	*6.7*	*7.0*	*17.6*	*25.0*	*0.22*	*2.05 (1.22–3.43)*	*0.006*
Overall mortality (%)	26.9	14.3	20.4	42.0	87.5	<0.001	2.48 (1.88–3.30)	<0.001
Patients without adjuvant chemotherapy	26.2	*15.0*	*23.3*	*44.1*	*75.0*	*0.002*	*2.49 (1.75–3.54)*	*<0.001*
Colon cancer mortality (%)	10.4	4.3	3.7	18.0	62.5	<0.001	3.40 (2.23–5.19)	<0.001
Patients without adjuvant chemotherapy	7.1	5.0	4.7	11.8	25.0	0.28	2.58 (1.24–5.34)	0.011

mHR hazard ratio adjusted for stage II subdivision (stage IIA/IIB/IIC, i.e. T3/T4a/T4b) and adjuvant chemotherapy status for metastatic recurrence

[a] Chi-squared test

[b] Aggregate score calculated in patients with data on all five characteristics (n = 182)

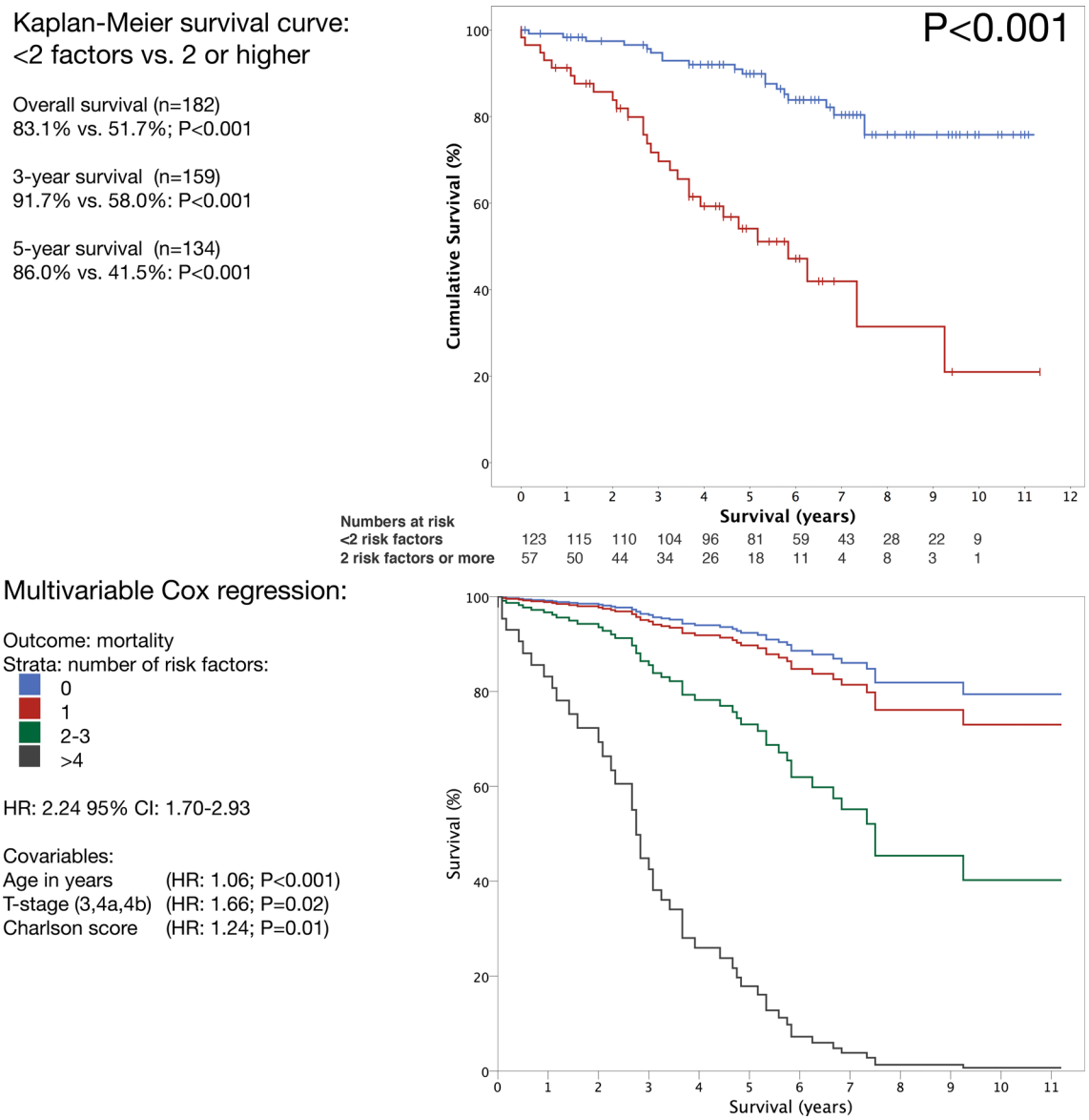

FIG. 2 Kaplan–Meier survival curve (univariate log-rank) and multivariable Cox proportional hazards survival estimates stratified over stage II risk scores. *HR* hazard ratio, *CI* confidence interval

more often than not[13] includes gastrointestinal symptoms, neutropenia, and sensory neuropathy, or, in extreme cases, can even be deadly.[14] In addition, overtreatment burdens healthcare with unnecessary costs, which amount to an estimated US$83,206.00 in mean additional total healthcare costs with the addition of FOLFOX, or US$39,916.00 for 5-fluorouracil/leucovorin.[15]

Although cost-effective as a whole,[16] the addition of a simple and universally applicable risk score that is based on readily available factors for most colon cancer patients may help in stratifying the risks and potential benefits, and support decision making if any uncertainties arise in an assessment solely based on the NCCN recommendations, based on lymph node yield, tumor grade, and resection margins. Our score used characteristics that have all been separately validated as known risk factors for recurrence and disease-specific mortality in colon cancer patients, i.e. high-grade disease, baseline CEA >5 ng/L,[17,18] LVI,[19] perineural invasion,[20] and EMVI.[21] The rationale for this selection was also that these factors would not overlap significantly and that they are part of the vast majority of baseline surgical pathological assessments of colon cancer patients.

Main Findings

Our most significant finding was that the number of high-risk factors present form strata that are incrementally associated with recurrence and mortality in stage II colon cancer patients, independently of stage II subcategory and adjuvant chemotherapy status. Therefore, this risk score stratification could serve as an additional risk assessment that should be weighed heavily in decisions regarding adjuvant treatment. The most significant infliction in terms of risk of recurrence happens at two risk factors or higher. For patients with one or no risk factors, recurrence rates were in the 7 % range, which rises dramatically to nearly 30 % recurrence in patients with two or more risk factors, including up to a one in four recurrence rate in those who had not received adjuvant treatment. These patients are potentially missing out on potential benefits of adjuvant treatment.

Weaknesses and Further Research

In terms of population characteristics, the sample was dominated by patients with stage IIA disease, which outnumbered stage IIB and IIC tumors combined by a 3:1 ratio, meaning that the results found here can mostly be considered valid for stage IIA patients. Further validation may be needed for stage IIB and IIC separately. On the other hand, these two groups are in fact already part of the minority of stage II patients where treatment recommendations tend to be more resolutely biased towards adjuvant treatment. Additionally, most findings of importance reach statistical significance thresholds nevertheless.

Another issue with the findings described here is that, largely due to the absence of baseline CEA values in approximately one-third of the stage II population (mostly patients from the earlier years of this cohort), a significant portion of patients could not have a stage II risk score computed. Follow-up research should validate this score in a cohort where all patients have a baseline CEA. This limitation will not be an issue in calculating risk scores in current colon cancer patients as measuring baseline CEA has become a standard element of preoperative assessment.

Lastly, the potential benefits and cost effectiveness of adjuvant chemotherapy needs to be evaluated in the context of this risk stratification. As this is a retrospective series, we cannot draw any meaningful conclusions on the effect of chemotherapy. A prospective population sample would be necessary to evaluate the usefulness of adjuvant treatment recommendations for each of the risk strata.

CONCLUSION

The colon cancer risk score introduced provides a prognostic tool that is based on readily available data extracted from baseline pathology and preoperative CEA, which provides an easy method to stratify risks of mortality and recurrence, and may therefore help in treatment decisions after surgery in stage II colon cancer patients.

DISCLOSURE None.

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