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Original Research

Baseline and postoperative C-reactive protein levels predict mortality in operable lung cancer

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Abstract ***Background:*** Higher blood levels of C-reactive protein (CRP) have been associated with shorter survival in patients with cardiovascular, chronic obstructive pulmonary disease and cancer. We investigated the impact of baseline and postoperative CRP levels on survival of patients with operable lung cancer (LC).

Patients and methods: CRP values at baseline (CRP_0) and 3 days after surgery (CRP_3) were measured in a consecutive series of 1750 LC patients who underwent complete resection between 2003 and 2015. Patients were classified as having 0 ($N = 593$), 1 ($N = 658$) or 2 ($N = 553$) risk factors: CRP_0 and/or CRP_3 values above the respective median value. The effect of higher CRP was evaluated by Kaplan–Meier mortality curves and adjusted hazard ratio (HR) with 95% confidence interval (CI), by fitting Cox proportional hazards models.

Results: Cumulative proportions of 5-year survival were 67% for 0 risk factors, 58% for 1 risk factor and 41% for 2 risk factors ($P < 0.0001$). The overall 5-year mortality risk was significantly higher in patients with 1 risk factor (adjusted hazard ratio [aHR] 1.43 [95% CI 1.14–1.79]), or 2 risk factors (aHR 2.49 [95% CI 1.99–3.11]). A significant impact on survival was observed in each tumour-node-metastasis stage group, and in the subset of non-smokers. Postoperative 30-

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day mortality was significantly higher in patients with 2 risk factors only (aHR 2.2% versus 0.6%, $p < 0.0475$).

Conclusions: Baseline and postoperative CRP levels predict immediate and long-term mortality in all stages of operable lung cancer. Patients with higher CRP levels could be candidate to randomised adjuvant trials with anti-inflammatory agents.

1. Introduction

Lung cancer (LC) is the leading cause of cancer death in men and the second one in women worldwide. In 2012, LC has occurred in 1.8 million people (13% of the world's total cancer incidence), leading to 1.6 million deaths (19% of all cancer deaths) [1]. The overall 5-year survival of LC patients remains dismal (<20%) [2], even though the 8th tumour-node-metastasis (TNM) staging system has outlined a better survival in stage I patients, compared to the previous version [3], possibly due to the improvement of screening programmes, staging algorithm, surgical treatment, targeted chemotherapy and immunotherapy, as well as patient selection. New discoveries on the relationship between immune system and cancer have expanded the prospects of LC patient stratification by immune-markers, related to both tumour and the host's immunological status [4]. On the first side, tumour immune microenvironment (TIM) has proved to play a prognostic role in several solid tumours, including LC [5]. This is particularly true for new targeted therapies that modulate tumour-microenvironment cells, expressing programmed cell death protein 1 (PD-1) and its ligand (PD-L1), thereby achieving a substantial tumour regression and prolonged disease stabilisation also in LC patients [6,7].

On the other side, different chemokines related to host's innate immune system have emerged as significant prognostic biomarkers. C-reactive protein (CRP) is the most common inflammatory marker used in routine clinical practice [8]. Elevated levels of circulating CRP are associated with an increased risk of LC in cancer-free individuals [9], as well as low-dose computed tomography screening participants [10], and the value of CRP in predicting disease progression and response to therapy has been widely explored in the setting of chronic inflammatory, cardiovascular and chronic obstructive pulmonary disease [11,12]. A recent meta-analysis outlined that higher baseline CRP level is associated with significantly poorer prognosis in resected LC [13], thereby suggesting that pretreatment CRP levels could be used as prognostic factors in early-stage LC, alone or in combination with other tumour or patient features [14].

In contrast, data on prognostic role of postsurgical CRP levels are lacking [15], and no studies have investigated the relationship and the impact of both baseline and postoperative CRP levels on the outcome of operable LC. The present study was designed to address this issue in a large series of patients with resected LC.

2. Methods

2.1. Study population

The current study included all patients who underwent a complete anatomical resection for primary LC at the Thoracic Surgery Division of the National Cancer Institute of Milan, from January 2003 to December 2015. Resections were performed mainly through lateral muscle-sparing thoracotomy and included pneumonectomy, (bi)lobectomy or anatomical segmentectomy, with systematic lymph node dissection. All patients were staged according to the 7th edition of International Association for the Study of Lung Cancer (IASLC) staging system [3].

2.2. Data collection and follow-up

Available data at baseline (surgery date) included age, gender, body mass index (BMI), percent predicted forced expiratory volume in the first second of expiration (FEV_1) and plasma level of CRP at baseline (CRP_0). In addition, CRP level was evaluated 3 days (CRP_3) after surgery, and the corresponding maximum value (CRP_{max}) after surgery was recorded. CRP was quantified by immunoturbidimetry using a Roche automated clinical chemistry analyzer (Roche Diagnostics, Belleville, NJ) from the same laboratory through the entire study period.

Of 2183 consecutive resections from 2001 patients, we excluded resections that did not have: (i) TNM stage of tumour (16 resections), (ii) CRP_0, and/or CRP_3, and/or CRP_{max} (272 resections) and (iii) follow-up information (15 resections). Of the remaining 1880 evaluable resections, we selected the cohort formed by 1750 patients who underwent their first resection during the considered period (Fig. A.1).

Each member of the study population accumulated person-years of follow-up from baseline until the date of death (all causes mortality being the outcome of interest for the current study) or till 26th June 2016 for survivors.

2.3. Statistical analysis

Descriptive statistics were used for summarising baseline and follow-up characteristics of the entire cohort. Scattergrams correlating log-transformed values of CRP_0 and CRP_3 (i.e. log CRP_0 and log CRP_3), were constructed and the corresponding Pearson's correlation coefficients were calculated.

Each individual patient was characterised according to whether the values of CRP were below or above the corresponding median values, respectively labelled as low or high CRP. Three CRP-based variables were tested. One, the so-called two levels of CRP-based variable contrasted (i) patients with high CRP_0 (or CRP_3) with (ii) those having low CRP_0 (or CRP_3). Two, the so-called three levels of CRP-based variable contrasted patients with (i) both high CRP_0 and CRP_3 (2 risk factors), (ii) high CRP_0 or high CRP_3 (1 risk factor) and (iii) both low CRP_0 and CRP_3 (0 risk factor). Finally, with the so-called four levels of CRP-based variable, patients on (i) high CRP_0 and high CRP_3; (ii) high CRP_0 and low CRP_3; (iii) low CRP_0 and high CRP_3 and (iv) low CRP_0 and low CRP_3, were also contrasted.

Kaplan–Meier curves picturing cumulative proportions of survivor according to the combination of high and/or low values of CRP_0 and CRP_3 were used. Time to event comparisons were made using log-rank test [16].

The prognostic value of CRP in predicting 5-year mortality was investigated by fitting Cox's proportional hazard regression models. The effects of two, three and four levels of CRP-based variables were separately investigated. The area under receiver operating characteristics curve, a summary measure of discrimination, was used as a primary performance metric of the considered models. We have also reported other metrics of improvement in fit, including the likelihood ratio test (for nested regression models). Model adjustments were made for age (continuous), gender, BMI (<25 or ≥ 25), FEV_1 ($\leq 90\%$ or $>90\%$), TNM stage (I, II or III) and resection type (pneumonectomy, lobectomy or segmentectomy). Cox models were fitted by considering the entire cohort and after stratification for TNM stage [17]. In addition, the prognostic value of CRP in predicting mortality was investigated for the portion of the included patients who had never smoked.

Thirty-day mortality and hospital stay for patients stratified according to the three levels of CRP-based variable was evaluated in terms of number and percentage or median and interquartile range, respectively.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

3. Results

Table 1 shows baseline and follow-up patient characteristics according to TNM stage. More than half subjects were men, with a median age of 66 years, BMI of 25 kg/m^2, and FEV_1 of 65%. Adenocarcinoma was the most frequent histologic type (63%) in all stages. There were substantial differences in resection volumes, values of CRP_3 and CRP_{max} and in number and percentage of 30-day deaths, as well as 5-year survivors, according to tumour stage. As expected, patients with stage I disease, compared to patients with stage III–IV, had a lower proportion of pneumonectomies (3.5% versus 19.4%), 30-day deaths (0.6% versus 1.5%) and a higher proportion of 5-year survivors (77.1% versus 40.6%). During follow-up, there were 661 deaths at 5 years.

Overall, CRP_0 and CRP_3 values were positively correlated (Fig. A.2, $P < 0.0001$). As reported in Table 2, an increased risk of 5-year mortality for CRP_0 and CRP_3 values taken individually (two-level CRP-based variable, models 1 and 2), as well as for their combination (three-level CRP-based variable, model 3), was found from the multivariable Cox model. Of interest, CRP_0 and CRP_3 levels independently predicted 5-year mortality since significant goodness-of-fit improvements were obtained contrasting model 3 with both models 1 and 2. Additionally, there seems to be a synergic effect of CRP_0 and CRP_3, since the combined observed effect (hazard ratio, HR = 2.49 model 4) exceeds that expected value according to model 3 (expected HR = 2.38).

The cumulative proportions of survivors at 5 years in the entire cohort were 67%, 58% and 41% among patients with 0, 1 and 2 risk factors, respectively (Fig. 1). The three levels of CRP-based variable predicted 5-year survival also in the subsets of 815 patients at stage I (Fig. 2a) and 204 non-smokers (Fig. 2b), with a cumulative survival of 79%, 63% and 59% ($P < 0.0001$) and 76%, 63% and 43% ($P < 0.0001$), respectively. Similar findings were found by considering the effect of the four levels of CRP-based variable (Fig. A.3).

The adjusted effects of the three levels of CRP-based variable on 5-year mortality according to the TNM stages and non-smokers are shown in Fig. 3. Compared with patients having 0 risk factors, those on 2 risk factors had consistent increased mortality in all subgroups, being the adjusted HRs 2.6 (95% CI 1.7–3.9), 3.2 (1.9–5.3) and 2.1 (1.5–2.9) among patients at I, II and III stages respectively, and 4.5 (1.9–10.6) among non-smokers.

When the impact of CRP on the immediate postoperative course was analysed (Table A.1), higher CRP_3 levels were associated with longer hospital stay (7

Table 1
Selected characteristics of study patients.

Characteristic	Overall cohort (N = 1750)	Stage I (N = 815)	Stage II (N = 410)	Stage III or IV (N = 525)
At baseline				
Age				
Mean (SD)	66 (9.3)	67 (8.7)	66 (9.3)	64 (9.9)
Gender				
Female	527 (30.1%)	258 (31.7%)	114 (27.8%)	155 (29.5%)
Male	1223 (69.9%)	557 (68.3%)	296 (72.2%)	370 (70.5%)
CRP_0 (mg/l)				
Median (IQ range)	3 (9)	3 (5)	5 (15)	4 (13)
FEV_1 (%)				
Median (IQ range)	65 (34)	65 (35)	63 (37)	65 (36)
BMI				
Median (IQ range)	25 (4)	25 (4)	25 (4)	25 (4)
Types of cancer				
Adeno	1099 (62.8%)	531 (65.2%)	225 (54.9%)	343 (65.3%)
Squamous	447 (25.5%)	204 (25%)	133 (32.4%)	110 (21%)
Other	204 (11.7%)	80 (9.8%)	52 (12.7%)	72 (13.7%)
Resection type				
Pneumonectomy	190 (10.9%)	28 (3.5%)	60 (14.6%)	102 (19.4%)
Lobectomy	1387 (79.7%)	671 (82.3%)	321 (78.3%)	395 (75.2%)
Segmentectomy	173 (9.9%)	116 (14.2%)	29 (7.1%)	28 (5.4%)
During follow-up				
CRP_3 (mg/l)				
Median (IQ range)	126 (108)	117 (102)	125 (109)	135 (115)
CRP_{max} (mg/l)				
Median (IQ range)	143 (111)	134 (107)	144 (115)	154 (110)
Thirty-day deaths				
N (%)	20 (1.1)	5 (0.6)	7 (1.7)	8 (1.5)
Five-year survivors				
N (%)	1089 (62.2)	628 (77.1)	248 (60.5)	213 (40.6)

SD, standard deviation; CRP_0, C-reactive protein measured at baseline; IQ, inter-quartile; FEV_1, percent predicted forced expiratory volume in the first second of expiration; BMI, body mass index.

versus 6 days, $P < 0.0001$), regardless of CRP_0, but the 30-day mortality was significantly higher only in patients with both $CRP_0 > 3$ and $CRP_3 > 126$ mg/l (2.2% versus 0.6%, $p < 0.0475$).

4. Discussion

In this large unselected series of resected LC cohort, our findings show that the values of CRP at baseline and at

Table 2
Relationship between C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3) and risk of death after 5 years from surgery.

CRP_0 (mg/l)	CRP_3 (mg/l)	Model 1	Model 2	Model 3	Model 4
		HR[c] (95% CI)	HR[c] (95% CI)	HR[c] (95% CI)	HR[c] (95% CI)
≤3		1.00 (reference)		1.00 (reference)	
>3		1.93 (1.63–2.27)		1.76 (1.53–2.15)	
	≤126		1.00 (reference)	1.00 (reference)	
	>126		1.57 (1.33–1.86)	1.36 (1.19–1.68)	
Zero risk factor					1.00 (reference)
One risk factor					1.43 (1.14–1.79)
Two risk factors					2.49 (1.99–3.11)
−2 LogL[a]		8254.264	8287.511	8238.313	8240.501
AUC[b]		0.81	0.83	0.81	0.81

CRP_0, C-reactive protein measured at baseline; CRP_3, C-reactive protein measured 3 days after surgery. Zero risk factor: $CRP_0 \leq 3$–$CRP_3 \leq 126$ mg/l; 1 risk factor: $CRP_0 > 3$–$CRP_3 \leq 126$ mg/l or $CRP_0 \leq 3$–$CRP_3 > 126$ mg/l; 2 risk factors: $CRP_0 > 3$–$CRP_3 > 126$ mg/l.

[a] Goodness-of-fit statistics.

[b] Area under the ROC curve.

[c] Adjusted hazard ratio, and 95% confidence interval, estimated Cox proportional hazard model. Adjustment was made for age, gender, body mass index, percent predicted forced expiratory volume in the first second of expiration, type of surgery and tumour size according to categories reported in Table 1.

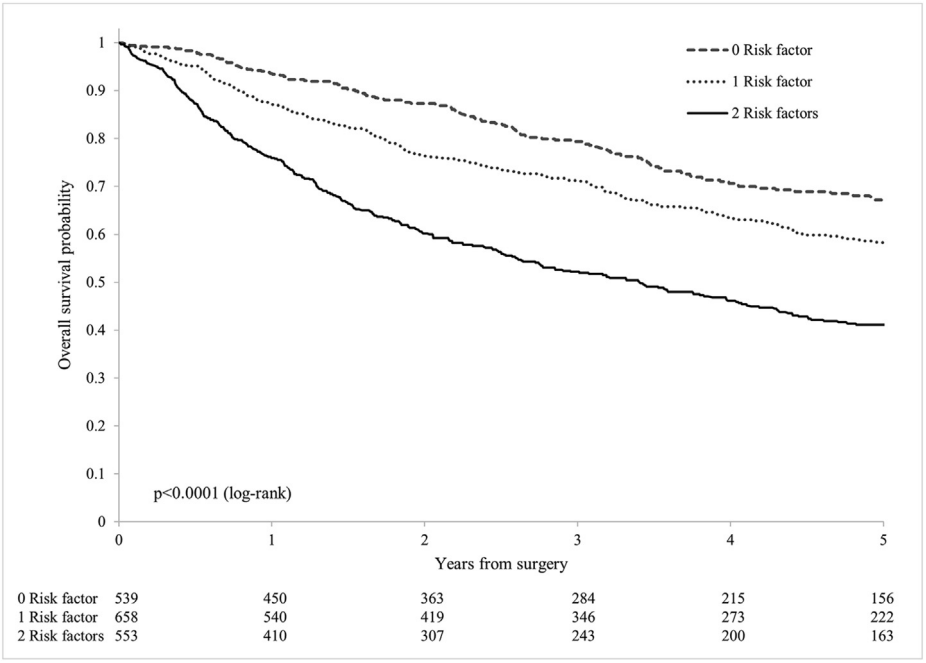

Fig. 1. Kaplan–Meier survival curves according to C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3). Zero risk factor: $CRP_0 \leq 3$–$CRP_3 \leq 126$ mg/l; 1 risk factor: $CRP_0 > 3$–$CRP_3 \leq 126$ mg/l or $CRP_0 \leq 3$–$CRP_3 > 126$ mg/l; 2 risk factors: $CRP_0 > 3$–$CRP_3 > 126$ mg/l.

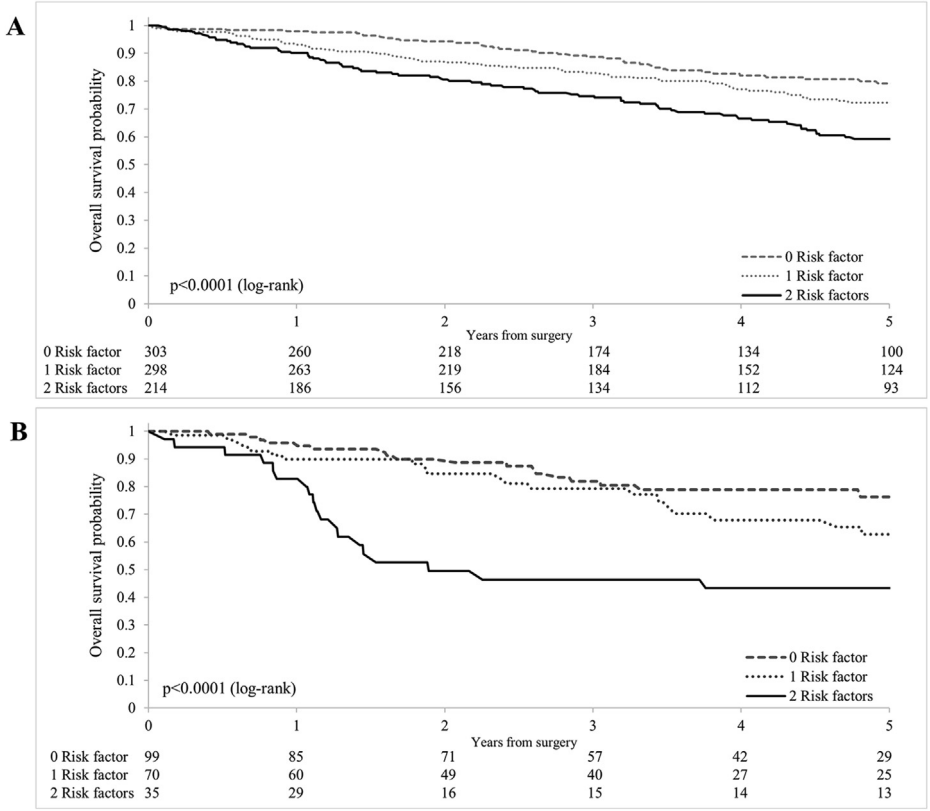

Fig. 2. Kaplan–Meier survival curves according to C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3), considering only (A) stage I tumours (B) or non-smoker individuals. Zero risk factor: $CRP_0 \leq 3$–$CRP_3 \leq 126$ mg/l; 1 risk factor: $CRP_0 > 3$–$CRP_3 \leq 126$ mg/l or $CRP_0 \leq 3$–$CRP_3 > 126$ mg/l; 2 risk factors: $CRP_0 > 3$–$CRP_3 > 126$ mg/l.

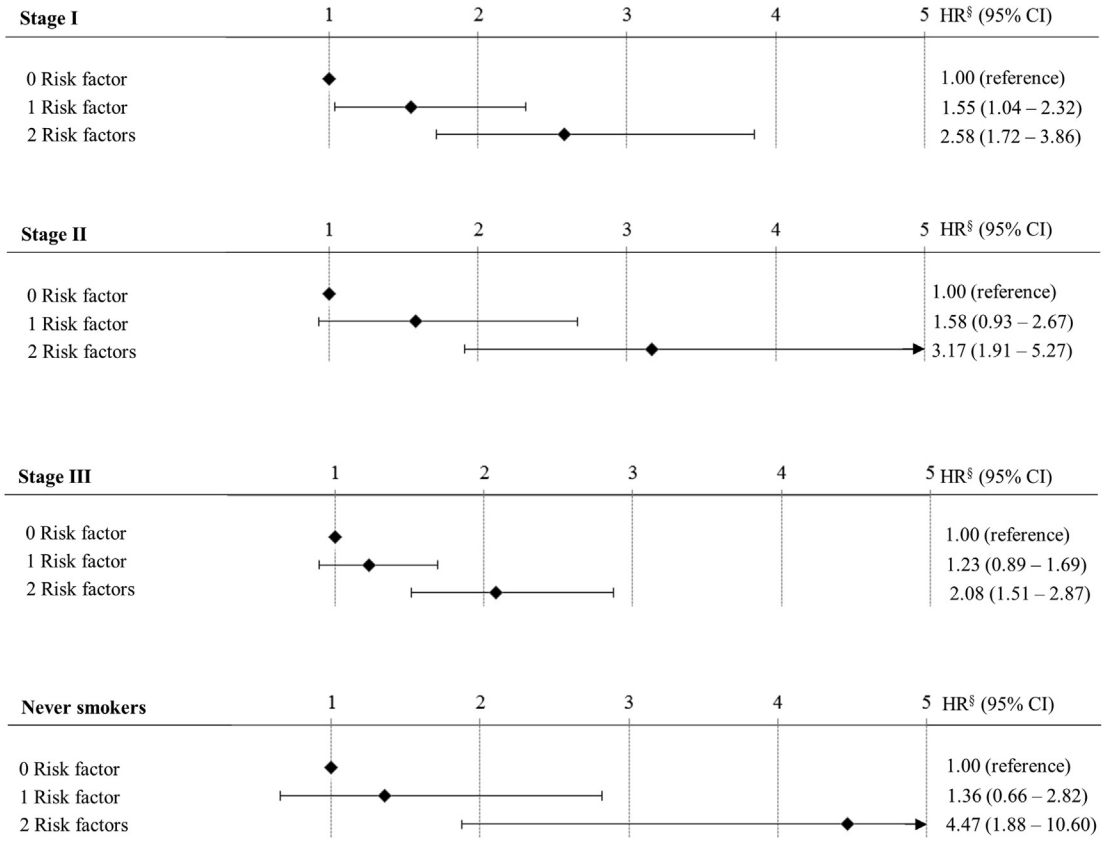

Fig. 3. Forrest plots showing the relationship between C-reactive protein measured at baseline (CRP_0) and 3 days after surgery (CRP_3) and the risk of death after 5-year from surgery according to stage and among never smokers. §Adjusted hazard ratio and 95% confidence interval estimated Cox proportional hazard model. Adjustment was made for age, gender, body mass index, percent predicted forced expiratory volume in the first second of expiration, type of surgery and tumour size according to the categories reported in Table 1.

3 days after surgery hold important prognostic information on overall 5-year mortality. Indeed, baseline and postoperative CRP levels predict immediate and long-term mortality in all stages of operable lung cancer. These results were confirmed in subgroup analyses restricted to patients with stage I, stage II, or stage III and non-smokers.

CRP is an acute-phase protein with a long half-life (about 19 h), that is similar under both physiological and pathological conditions, directly reflecting the rate of its synthesis and the intensity of the pathological processes [18]. During acute-phase reaction, CRP is secreted by hepatocytes (to a lesser degree by kidney, endothelial and vascular smooth muscle cells, monocytes and neutrophils) [19] in response to tissue damage and activity of different cytokines (interleukin-6 [IL6], interleukin-1 [IL1] and tumour necrosis factor [TNF]-α) [20].

More specifically, CRP binds to the surface of apoptotic cells, invading microbes or 'altered' cells and activates the classic complement pathway, enhancing opsonization and phagocytosis of CRP-tagged targets [21,22]. On the other hand, CRP recruits C4b-binding protein (the major inhibitor of the classic pathway) and modulates the activity of immune cells (neutrophils, monocytes and macrophages) [19]. Thus, although some of its functions still remain unclear, CRP is today considered a 'modulator' of innate immunity, rather than a mere indicator of inflammation.

Baseline CRP has been validated as prognostic marker in a variety of solid tumours [8], including LC [14], but the reason for such a prognostic effect is still unclear. Several mechanisms have been hypothesised to explain this association: (i) CRP is a marker of chronic inflammation that causes DNA injury and weakening of the immune system, enhancing carcinogenesis and tumour progression [23]; (ii) tumour cells and TIM may release several cytokines and chemokines, thus resulting in inflammatory cell infiltration into the cancer microenvironment and increasing the serum CRP concentrations [24]; (iii) tumour growth itself may cause inflammation of surrounding tissue [15] and (iv) the host may produce higher CRP levels as a result of immune response [25].

Our results confirm the predictive value of preoperative CRP on long-term survival, but for the first time demonstrate that postsurgical levels of CRP have an independent effect on the immediate and long-term outcome. In fact, even though Pearson's analysis

showed a statistically significant correlation between CRP_0 and CRP_3, the two risk factors maintained their individual predictive value, with a significantly higher risk of 30-day and 5-year mortality for patients with a rise of both preoperative and postoperative CRP.

In this scenario, the role of tumour microenvironment in modulating host's immune status is intriguing, as recent observations revealed that tumour–host interactions extend well beyond the local tissue microenvironment, and tumours not only respond to, but actively perturb host organs at distant anatomic sites. Specifically, it's the TIM heterogeneity (defined according to density, location and organisation of immune cell types and cytokines) that plays a significant role in cancer prognosis [26]. In the setting of Non-Small Cell Lung Cancer (NSCLC), some authors have recently documented that the combination of low CD4/CD8/C68-positive cell density and PD-L1 score higher than five in malignant cells could help in identifying small subset of lung adenocarcinomas with worse outcomes [6]. This heterogeneity is related to the density of specific stromal cells into TIM as well [27]. It has been reported that cancer-associated fibroblasts (a subset of stromal cells) secrete IL6 that enhances epithelial-to-mesenchymal transition changes in NSCLC cells: this transformation results in increased chemoresistance and worse outcome [28]. Thus, it is not surprising that higher levels of chemokines secreted by TIM (such as IL6 that increases also plasmatic CRP levels) are associated with worse NSCLC prognosis [29]. Based on the results of the present study, CRP could be also considered as a marker of a 'sick' tumour microenvironment, confirming an 'evolving' and active interaction between host's innate immune system, TIM and cancer. Further studies are needed to better explore the value of this association.

In the field of inflammation, reduced circulating levels of miR-16-5p have been correlated with increased serum CRP concentration [30]. Similarly, recent data indicated that miR-21, released by cancer cells, may induce the secretion of pro-inflammatory cytokines (such as TNF and IL6), suggesting a direct link between miR-21 expression levels and inflammatory response. As a result, miR-21 is directly associated to CRP levels as well [31]. These findings may open the door to future studies evaluating the role of microRNAs (miRNAs) as biomarkers of inflammation and prognosis in the setting of LC patients [32]. This issue is particularly appealing considering that extracellular miRNAs are easily-measurable in the circulation and, owing to their stability, are increasingly reported as potential diagnostic and prognostic biomarkers for different diseases [33].

The 8th TNM system has further refined the predictive value of LC staging, by the use of anatomical risk stratifies, thereby expanding the proportion of patients that are candidate to adjuvant therapy [4]. However, none of the adjuvant treatment schedules now in clinical practice are focussed against pro-tumourigenic microenvironment. The results of our study confirm that the evaluation of host's immune hyperactivity (related to baseline and postoperative CRP level) could be added to the clinical work-up to better categorise LC patients (as low- or high-risk), refine the probability of life-threatening postoperative complications and guide the decision to administer or not an adjuvant therapy. In addition, the putative pro-inflammatory and/or immune-deficient status identified by higher CRP levels, could represent the target of specific interventions in the adjuvant setting.

Taking into account prior evidence that CRP levels can be lowered by metformin or statins [34,35], the present results open new prospects for adjuvant chemoprevention in operable LC patients. Baseline and postoperative CRP levels could be used to define candidates to randomised adjuvant trials, testing the efficacy of anti-inflammatory agents, such as COX-2 inhibitors, metformin or statins, with the aim of reducing all-cause mortality in resected LC patients, with or without prior adjuvant chemotherapy. Prospective trials could also investigate the value of CRP as a reliable intermediate biomarker, to predict the long-term effects of such intervention.

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Conflict of interest statement

None declared.

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Appendix G. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.03.020.

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