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Preoperative hemoglobin count and prognosis of esophageal cancer, a population-based nationwide study in Finland

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ABSTRACT

Background: The prognostic value of preoperative hemoglobin in patients undergoing esophagectomy is unknown. The aim of this study was to examine whether preoperative hemoglobin is associated with prognosis in patients undergoing esophagectomy for cancer.
Materials and methods: This was a population-based nationwide retrospective cohort study in Finland, using Finnish National Esophago-Gastric Cancer Cohort (FINEGO). Esophagectomy patients with available preoperative hemoglobin measurement were included. Multivariable cox regression provided hazard ratios (HR) with 95% confidence intervals (CI), adjusted for calendar period of surgery, age at surgery, sex, comorbidity (Charlson Comorbidity Index), tumor histology, tumor stage, neoadjuvant therapy, type of surgery (minimally invasive or open) and annual hospital volume.
Results: Of the 1313 patients, 932 (71.0%) were men and 799 (60.9%) had esophageal adenocarcinoma. Overall all-cause mortality was significantly higher in the lowest hemoglobin count tertile (HR 1.26 (1.07–1.47)) compared to the highest tertile, but this association was attenuated after adjustment for confounding. No differences were found between the preoperative hemoglobin groups in the adjusted analyses of 90-day all-cause, 5-year all-cause, and 5-year cancer-specific mortality.
Conclusion: In this population-based nationwide study, preoperative hemoglobin count had no independent prognostic significance in esophageal cancer.

1. Introduction

Esophageal cancer is the 6th most common cause of cancer-related death globally and the overall 5-year survival is less than 20% [1]. Surgery for esophageal cancer can improve 5-year survival to 40–50% [2]. The strongest determinant of survival is tumor stage [2,3].

Different combinations of laboratory values, such as neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI) have been associated with prognosis in esophageal cancer after surgery, but less studies exist on hemoglobin [4]. Perioperative allogenic blood transfusion in an attempt to correct hemoglobin and hematocrit values prior to esophagectomy is associated with poor prognosis [5]. Lower hemoglobin levels might result in poor tissue oxygenation after surgery, and thus result in anastomotic leaks or other complications, which in turn are associated with poor long-term prognosis [6,7]. A previous study found no association between hemoglobin count and prognosis after esophageal cancer treatment [8]. The study was rather small (n = 468), and included a selected group of patients. Therefore, it is unknown whether preoperative hemoglobin count is associated with prognosis after esophageal cancer surgery.

The aim of the present study was to assess whether preoperative blood hemoglobin count is associated with prognosis after esophageal cancer surgery. As nutritional problems, transfusions and complications are associated with worse prognosis, it was hypothesized that lower preoperative hemoglobin count is also associated with worse prognosis of esophageal cancer.

2. Methods

2.1. Study design

This was a population-based nationwide retrospective cohort study based on the Finnish National Esophago-Gastric Cancer

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Cohort (FINEGO) [9]. The esophageal cancer cohort includes all esophageal cancer patients that underwent resectional surgery in Finland between years 1987 and 2016 [10]. For this study, only patients undergoing esophagectomy and those with preoperative hemoglobin available were included. Ethical committee in Northern Osthrobothnia (EETMK 115/2016).

2.2. Data sources

The patients were identified from the Finnish Cancer Registry and Patient Registry, which are highly complete for esophageal cancer [11]. These registries were also used for defining calendar year of surgery, annual hospital volume of cancer surgery, and patient age, sex and Charlson comorbidity index (Royal College of Surgeons edition) [12]. Medical and pathology records, as well as surgical charts were retrieved for the identified patients, and evaluated for a multitude of clinical and medical variables by expert upper gastrointestinal surgeons, including tumor histology, tumor stage according to the 8th edition of TNM classification [13], neoadjuvant therapy, and type of surgery (minimally invasive, or open). Some variables, such as preoperative laboratory values were obtained by a trained study nurse. The data collection and variables were decided upon by a consensus in the collaborative group. Statistics Finland provided 100% complete follow-up data on mortality until December 31, 2019.

2.3. Exposure (blood hemoglobin count)

The exposure of this study was hemoglobin count in mg/l, which was divided in to three subgroups (ie. tertiles), the highest tertile being the reference group.

2.4. Outcome

The primary outcome was overall all-cause mortality, and secondary outcomes were 90-day all-cause mortality, 5-year all-cause mortality, and 5-year cancer-specific mortality, counted from the date of surgery until the end of specified follow-up time, death, or December 31, 2019 (December 31, 2018 for cancer-specific mortality), whichever occurred first.

2.5. Statistical analysis

All analyses were done according to an *a priori* study protocol. Multivariable cox regression provided hazard ratios (HR) with 95% confidence intervals (CI). The crude model was not adjusted for confounders. Model 2 was adjusted for confounding variables including: 1) calendar period of surgery (1987–1996, 1997–2006, or 2007–2016), 2) age at surgery (continuous variable), 3) sex: male, or female, 4) comorbidity (Charlson Comorbidity Index score 0, 1, or $\geq$2), 5) tumor histology (adenocarcinoma, or squamous cell carcinoma), 6) tumor stage (0-I, II, III, or IV), 7) neoadjuvant therapy (yes, or no), 8) type of surgery (minimally invasive, or open-surgery) and 9) annual hospital volume (in tertiles: $\leq$ 25, 26-72, or 73-141 per 4 years). For missing data (up to 7.1% patients had missing data on either histology, tumor stage, and/or neoadjuvant therapy), both complete case analysis and multiple imputation were conducted. Imputation variables included all confounding variables categorized as above, and all-cause mortality. The number of imputed datasets was 20 and fully conditional specification was used under the assumption that the data were missing at random. Due to similar results using complete case analysis and multiple imputation, only HRs and 95% CIs from the multiple imputation are presented. A post-hoc sensitivity analysis including only patients treated during the last time period where there were only eight missing patient records and 4.3% missing hemoglobin values, adjusted for the confounders above, was done to explore the potential selection bias due to missing hemoglobin values during the first two periods could affect the results. All statistical analyses were calculated using IBM SPSS 26 (Armonk, NY).

3. Results

3.1. Patients

A total of 2045 patients with esophagectomy and a cancer diagnosis were identified in the registries. Of these, 1568 patients' records were available for analysis and a curative intent esophagectomy for cancer could be confirmed for 1456 patients during the study period. One-thousand-three-hundred-thirteen had blood hemoglobin count data available within three days before surgery and were analyzed. Proportion of men was higher with 932 patients (71.0%), and 799 (60.9%) of all patients had adenocarcinoma. The majority of men (39.9%) were in the highest preoperative hemoglobin tertile, while the majority of women (42.0%) were in the lowest tertile (see Table 1).

3.2. Primary outcome

In the unadjusted analysis, overall all-cause mortality was significantly higher in the lowest tertile (HR 1.26, 95% CI 1.07–1.47) compared to the highest tertile (Table 2). After adjustment for known prognostic factors, this association between hemoglobin count and prognosis was attenuated (adjusted HR 1.14, 95% CI 0.96–1.35) (Table 2.) In the post-hoc adjusted sensitivity analyses including only patients from the last time period of 2007–2016, no differences in overall all-cause mortality between the exposure groups (adjusted HR 1.15, 95% CI 0.88–1.52, lowest versus highest tertile) were observed.

3.3. Secondary outcomes

For 90-day all-cause mortality, no association between hemoglobin count and prognosis was observed in any of the analyses. In the unadjusted analysis, low preoperative hemoglobin count was significantly associated with high 5-year all-cause mortality (HR 1.19, 95% CI 1.00–1.42) and 5-year cancer-specific mortality (HR 1.23, 95% CI 1.02–1.47). After adjustment for the confounders, these associations were attenuated (Table 2.). In adjusted sensitivity analyses including only patients from the last time period of 2007–2016, there were no differences in 90-day all-cause (adjusted HR 1.06, 95% CI 0.44–2.58), 5-year all-cause (adjusted HR 1.16, 95% CI 0.87–1.56), or 5-year cancer-specific mortality (adjusted HR 1.14, 95% CI 0.83–1.55) comparing the lowest versus the highest tertile.

4. Discussion

The results of the present study indicate that preoperative hemoglobin count was associated with improved outcomes after esophageal cancer surgery, but this association was mitigated after adjustment for relevant prognostic factors. Therefore, hemoglobin count seems to have no independent prognostic significance in esophageal cancer.

The strengths of this study include its size, being by far the largest study on the topic, allowing robust analysis of estimates, and population-based design, reducing selection bias. Additionally, the complete ascertainment of known preoperative prognostic variables allowed adjustment for all significant confounding variables. The follow-up was complete with no missing outcome data. There are also weaknesses. A significant proportion of patients with

Table 1
Characteristics of the 1313 patients who underwent esophagectomy for cancer, stratified into tertiles by preoperative hemoglobin count.

	Preoperative hemoglobin count (g/l)			
	70–125 N (%)	126–140 N (%)	141–183 N (%)	Total
Total	436 (33.2)	434 (33.0)	443 (33.7)	1313 (100)
Calendar period				
1987–1996	58 (24.6)	81 (34.3)	97 (41.1)	236 (18)
1997–2006	136 (32.9)	124 (30.0)	154 (37.2)	414 (31.5)
2007–2016	242 (36.5)	229 (34.5)	192 (29.0)	663 (50.5)
Age at surgery (Median [IQR])	66 [59-72]	65 [58-71]	64 [57-70]	65 [58-71]
Sex				
Male	276 (29.6)	284 (30.5)	372 (39.9)	932 (71.0)
Female	160 (42)	150 (39.4)	71 (18.6)	381 (29.0)
Comorbidity				
0	255 (30.9)	265 (32.1)	306 (37.0)	826 (62.9)
1	123 (37.3)	116 (35.2)	91 (27.6)	330 (25.1)
2 or more	58 (36.9)	53 (33.8)	46 (29.3)	157 (12.0)
Tumor histology				
Adenocarcinoma	256 (32.0)	251 (31.4)	292 (36.5)	799 (60.9)
Squamous cell	160 (34.7)	165 (35.8)	136 (29.5)	461 (35.1)
Missing	20 (4.6)	18 (4.1)	15 (3.4)	53 (4.0)
Tumor stage				
0-I	103 (27.5)	127 (33.9)	145 (38.7)	375 (28.6)
II	73 (33.3)	78 (35.6)	68 (31.1)	219 (16.7)
III	181 (36.7)	159 (32.3)	153 (31.0)	493 (37.5)
IV	50 (35.2)	43 (30.3)	49 (34.5)	142 (10.8)
Missing	29 (6.7)	27 (6.2)	28 (6.3)	84 (6.4)
Neoadjuvant therapy				
Yes	216 (45.9)	180 (38.2)	75 (15.9)	471 (35.9)
No	215 (25.8)	252 (30.3)	365 (43.9)	832 (63.4)
Missing	5 (1.1)	2 (0.5)	3 (0.7)	10 (0.8)
Type of surgery				
Minimally invasive	110 (39.6)	93 (33.5)	75 (27)	278 (21.2)
Open	326 (31.5)	341 (32.9)	368 (35.6)	1035 (78.8)
Annual hospital volume				
Lowest tertile	125 (28.5)	141 (32.1)	173 (39.4)	439 (33.4)
Middle tertile	143 (32.7)	159 (36.4)	135 (30.9)	437 (33.3)
Highest tertile	168 (38.4)	134 (30.7)	135 (30.9)	437 (33.3)

Table 2
Preoperative hemoglobin count and the risk of mortality after esophagectomy for cancer, expressed as hazard ratios (HR) with 95% confidence intervals (CI).

	No. patients	Preoperative hemoglobin count		
		70–125 g/l HR(95% CI)	126–140 g/l HR(95% CI)	141–183 g/l HR(95% CI)
Overall all-cause mortality				
Crude	1313	1.26 (1.07–1.47)	1.04 (0.88–1.21)	1.00 (reference)
Adjusted[a]	1313	1.14 (0.96–1.35)	0.98 (0.83–1.17)	1.00 (reference)
90-day all-cause mortality				
Crude	1313	1.14 (0.71–1.84)	0.99 (0.60–1.62)	1.00 (reference)
Adjusted[a]	1313	1.35 (0.81–2.26)	1.14 (0.68–1.91)	1.00 (reference)
5-year all-cause mortality				
Crude	1313	1.19 (1.00–1.42)	0.98 (0.82–1.18)	1.00 (reference)
Adjusted[a]	1313	1.12 (0.92–1.35)	0.97 (0.80–1.17)	1.00 (reference)
5-year cancer-specific mortality				
Crude	1313	1.23 (1.02–1.47)	0.95 (0.78–1.15)	1.00 (reference)
Adjusted[a]	1313	1.15 (0.95–1.41)	0.93 (0.76–1.14)	1.00 (reference)

[a] Adjusted for confounding variables time period, age, sex, comorbidity, tumor histology, tumor stage, neoadjuvant therapy, type of surgery, and annual hospital volume.

completely missing records and missing hemoglobin count, mostly during the earlier years of the study, might have caused some selection bias. This weakness was taken into account by adjusting for the year of surgery, and conducting a sensitivity analysis including only the latest time period where the records and the data was highly complete. Furthermore, missing confounder data were handled with multiple imputation. Both sensitivity analysis and multiple imputation showed results similar to the main analysis. Due to no available data on transfusions in these patients, transfusions could not be assessed. Transfusions are, however, on the hypothesized causal pathway between hemoglobin and death and cannot be classified as confounders in these analyses.

There are only few previous studies on hemoglobin count and prognosis in esophageal cancer. A retrospective Chinese study on preoperative blood count in esophageal squamous cell cancer (ESCC) patients undergoing esophagectomy (n = 468) found no association between hemoglobin and prognosis [8]. Patients with severe complications or 30-day mortality, preoperative systemic inflammatory response syndrome, neoadjuvant radiotherapy or chemotherapy and/or evidence of infection or autoimmune disease were excluded from the Chinese study [8], potentially severely biasing the results. A Spanish study (n = 85) suggested that low hemoglobin was associated with poor survival after radical surgical (n = 16) or non-surgical treatment of esophageal carcinoma [14]. This Spanish study was very small and heterogeneous, preventing any valid conclusions. In the present study, hemoglobin count was not associated with prognosis after adjustment for confounding.

The observed lack of association between hemoglobin and mortality in esophageal cancer is surprising, given that meta-analyses of observational studies in other cancer types have suggested an association [15–17]. However, previous large studies in prostate [18] and rectal cancers [19] have also suggested that preoperative anemia is not strongly or at all associated to overall survival. It is debatable if anemia is a marker of underlying comorbidity and inflammatory state related to cancer, or directly related to slow bleeding from the tumor in the gastrointestinal tract, or neoadjuvant therapy [20,21]. Anemia could be further classified using for example red cell distribution width (RDW). Unfortunately, specific data on red cell properties were not

available in this study and could not be assessed. Nevertheless, iron deficiency and anemia are prevalent in colorectal cancer patients [22]. For treatment of iron deficiency and anemia, the European Society for Medical Oncology (ESMO) guidelines recommend intravenous iron infusions, correction of underlying other causes and erythropoietin treatment, as well as transfusions [23].

Anemia is very common among cancer patients and its cause is often multifactorial: the direct effect of the malignancy, secondary to the malignancy, the effect of the treatment, and other factors [24]. Among lung cancer patients the degree of anemia was significantly related to duration of disease [25]. Also survival time was longer among those without anemia compared to the ones with anemia [25]. A Japanese study of patients with resectable esophageal cancer found an association between blood transfusions and decreased survival [26]. Also a meta-analysis of single-center observational studies found that receiving blood transfusions was a risk factor for worse long-term survival in patients undergoing esophagectomy for cancer [27]. Similar results have been published regarding colorectal cancer [28]. Based on these studies and the mitigation of association observed in this study it seems that the confounding factors, such as comorbidity and tumor stage, are more important mediators for prognosis than the hemoglobin itself. Also, a low preoperative hemoglobin count preoperatively might predispose clinicians to giving transfusions during or after surgery more easily, which in turn might worsen the prognosis. Again, these transfusions could be associated with confounding factors that are more important for prognosis than the transfusion itself. Unfortunately, no data on transfusions were available in this study and this could not be further explored.

This study has both clinical and research implications. Low hemoglobin count is not a poor prognostic factor but optimization of hemoglobin is still recommendable prior to surgery, in accordance with the current guidelines. Prospective studies should attempt to clarify whether iron infusions to correct hemoglobin preoperatively has long-term mortality benefits. Future research should also explore the potential benefits and harms associated with transfusions, as well as the threshold levels of hemoglobin for safe esophageal surgery.

In this population-based nationwide study, preoperative hemoglobin count does not appear to be independently associated to short- or long-term mortality after esophageal cancer surgery.

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CRediT authors contribution statement

Ella M.K. Jokela: Writing – original draft. **All FINEGO authors:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Joonas H. Kauppila:** Formal analysis, Resources, Data curation, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors report no conflicts of interest.

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Due to current legislation, the original data cannot be made publicly available. The data may be accessed after this has been approved by the relevant government and institutional bodies, and the authors can help in this process. The study or statistical analysis were not pre-registered in any independent institutional registry.

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