BMJ Open

Meta-analysis of the prognostic value of pretreatment serum ferritin in hepatobiliary and pancreas (HBP) cancers

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ABSTRACT

Background and objectives Studies have shown that serum ferritin (SF) has unfavourable prognostic value in hepatobiliary and pancreas (HBP) cancers. This meta-analysis aimed to comprehensively assess the prognostic role of pretreatment SF in patients with HBP cancers.

Methods Eligible studies published before January 2020 were obtained through a comprehensive search in the PubMed, Web of Science, Cochrane Library and EMBASE databases. Pooled HRs and 95% CIs were then employed as effect sizes.

Results Seven studies comprising 1244 patients were pooled. Elevated pretreatment SF was associated with worse overall survival (OS) (HR 1.60, 95% CI 1.36 to 1.88, p<0.001) and recurrence-free survival/progression-free survival/time to recurrence (HR 1.70, 95% CI 1.15 to 2.52, p=0.008). Significant prognostic value of elevated pretreatment SF on OS was detected in the subgroups regardless of the cancer type, race, SF cut-off value, tumour-node-metastasis stage and Newcastle-Ottawa Scale score.

Conclusion Elevated pretreatment SF was associated with worse survival outcome of patients with HBP cancers. As such, it may serve as a novel prognostic biomarker for HBP cancers.

INTRODUCTION

Hepatobiliary and pancreas (HBP) cancers include hepatocellular carcinoma (HCC), pancreatic cancer (PC) and biliary tract cancers. Biliary tract cancers range from those affecting the gall bladder, ampulla of Vater cancers as well as intrahepatic and extrahepatic cholangiocarcinomas. HBP cancers are one of the most common causes of cancer-related deaths in many countries.[1] Currently, the morbidity and mortality rates of HBP cancers across the world are rising rapidly.[1] These cancers are characterised by a poor overall survival (OS) and a high recurrence rate even when diagnosis and treatment are performed during the early stages of the disease. Unfortunately, majority of the patients are diagnosed at terminal stage of HBP cancers.[2–7] Despite rapidly developing research on diagnosis and treatment of HBP

Strengths and limitations of this study

► This study is the first systematic meta-analysis based on a comprehensive literature search to assess the prognostic value of serum ferritin in patients with hepatobiliary and pancreas (HBP) cancers.
► The results were systematically synthesised to overcome the shortcoming of a small-scale study, which reported the association between serum ferritin and HBP cancers.
► Limitations of the study will be the lack of robust clinicopathological data, the inclusion of different treatment modalities, the retrospective nature of the included studies and the publication bias among included publications.

cancers, their prognosis is still dismal. Cognisant to this, it is necessary to identify more valuable biomarkers to enable effective HBP cancer prognosis and design of optimised treatment strategies.

Serum ferritin (SF) is a major iron-binding protein that plays a critical role in tumour angiogenesis, proliferation and immune regulation.[8–10] Studies have found that iron may possess the ability to induce mutations, mediated through free radical generation or promote tumorigenesis through nutritional mechanisms.[11 12] Iron accumulation in the liver is an auxiliary factor that causes liver injury and hepatocarcinogenesis.[13] Elevated SF can reveal excessive iron load. High SF has been reported to be closely associated with inflammation, liver disease and cancer.[8 10 14–16] Previous studies have demonstrated that high SF is associated with worse prognosis in lung cancer, colorectal cancer, PC and peripheral T-cell lymphoma.[10 17–19] However, the prognostic role of SF in HCC is controversial.[20 21]

To date, no meta-analysis has been conducted to assess the prognostic role of SF in HBP cancers. Herein, a meta-analysis was conducted to identify the prognostic role of pretreatment SF in HBP cancers.

MATERIALS AND METHODS

Search strategies

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement-compliant systematic literature search for HBP cancer-related articles was conducted in the PubMed, EMBASE, Web of Science and Cochrane Library databases. The search was set to identify articles published from January 1970 to January 2020. The search terms used were: 'hepatocellular carcinoma', 'liver cancer', 'HCC', 'cholangiocarcinoma', 'biliary tract cancer', 'gallbladder cancer' and 'pancreatic cancer'. In the same line, free words adopted were: 'ferritin', 'isoferritin', 'prognosis', 'prognostic' and 'survival'. References from relevant articles were manually screened and retrieved for eligible studies. The PRISMA checklist is provided in online supplemental file 1, and the complete search strategy for HBP cancer-related articles can be found in online supplemental file 2.

Inclusion criteria

A study was included for meta-analysis if: (1) diagnosis of HBP cancers had been confirmed based on clinicopathological data, (2) the study evaluated the relationship between pretreatment SF and OS, recurrence-free survival (RFS)/progression-free survival (PFS) or time to recurrence (TTR), and (3) the study presented the cutoff value of SF.

Exclusion criteria

Studies were excluded if they were: (1) letters, case reports, reviews, abstracts, non-clinical studies or comments, (2) non-English articles, (3) studies presenting insufficient data for calculating the HR and 95% CI, and (4) studies with duplicate data or repeat report.

Data extraction and assessment of the risk of bias

Two reviewers independently screened all included articles and extracted the relevant data. Any disagreement was resolved by consulting with a third reviewer. Data collected from each study included name of first author, year of publication, study region, type of publication, cancer type, number of patients involved, time of follow-up, treatment modality used, patient age, SF cutoff value, disease stage, survival analysis method (univariate or multivariate) and survival outcome (OS, PFS, RFS and TTR). HRs with their 95% CIs were extracted from the univariate or multivariate survival analysis method or calculated from Kaplan-Meier survival curves.[22]

Quality evaluation of each included study was done using the Newcastle-Ottawa Scale (NOS).[23] The NOS includes eight items categorised into three: case selection (0–4 points), group comparability (0–2 points) and clinical outcome (0–3 points). Studies with a NOS score greater than or equal to 6 were defined as high-quality studies.[23]

Statistical analysis

The meta-analysis was done using the STATA statistical software V.15.1 (STATA, College Station, Texas).
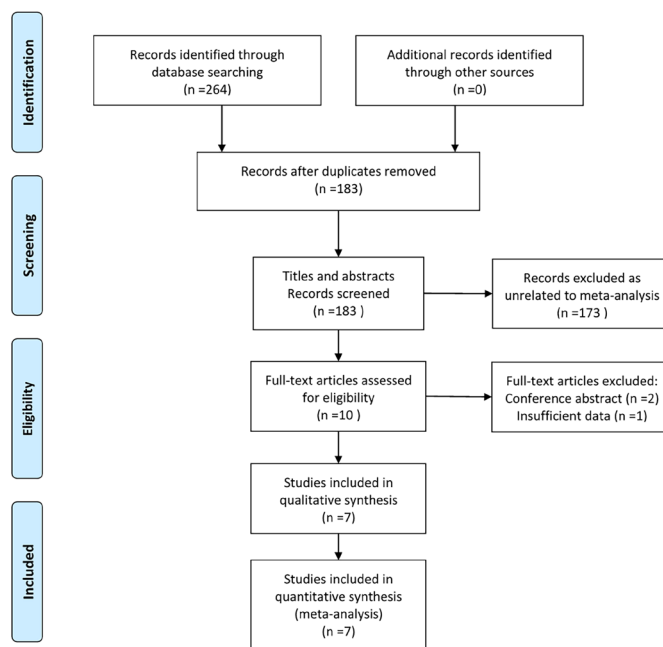
Figure 1 Flow chart of the included studies.

Cochran's Q test and I^2 test were employed to estimate the statistical heterogeneity between studies.[24] A p value <0.1 for Cochran's Q test or an I^2 value more than 50% (>50%) was defined as significant heterogeneity.[25] In cases of significant heterogeneity, the random effects model was employed to calculate the pooled result. Otherwise, the fixed effects model was applied. HRs with 95% CI were extracted from the included articles or calculated according to the methods reported by Tierney *et al* and Parmar *et al*.[22 26] The HRs were then pooled to assess the prognostic outcome. Subgroup analyses were conducted based on the cancer type, race, SF cut-off value, tumour-node-metastasis (TNM) stage and NOS score to detect the sources of heterogeneity. Sensitivity analyses were also undertaken to assess the stability of the pooled results. P values <0.05 indicated that there were statistically significant differences between groups.

Patient and public involvement

There was no patient or public involvement in the development of this research.

RESULTS

Search results

Search results and process are highlighted in figure 1. Two hundred and sixty-four relevant articles were identified from the database search. One hundred and eighty-three articles remained after eliminating the duplicates (81 articles). The 183 articles were reviewed by checking their titles and abstracts for eligibility. Among them, 173 articles were removed because they were unrelated to the study subject. The 10 articles remaining underwent full-text screening. Three of them were excluded because they were conference abstract and thus had

insufficient data. Finally, the seven studies remaining comprising 1244 patients were included in the meta-analysis.[16 19–21 27–29]

Characteristics of the included studies

The full texts of the seven studies included for meta-analysis had been published between 2014 and 2019. Most of the included studies were retrospective. Three studies were based in China, and the rest in Japan, Korea, USA and Italy. Three studies focused on HCC, two focused on PC while the other two focused on intrahepatic cholangiocarcinoma (ICC) and hepatobiliary cancer (HBC), respectively. The number of patients in each study ranged from 79 to 427. All seven studies revealed the association between pretreatment SF and OS. Four studies also reported RFS/PFS/TTR data. PFS in one study had been calculated using the Kaplan-Meier method.[19] The cut-off values of SF were between 200 and 840. HRs with 95% CIs were directly obtained from the seven studies through univariate and/or multivariate analyses. The NOS scores of the included studies ranged from 5 to 9. The specific features of the included studies are described in table 1.

Meta-analysis

SF and OS in HBP cancers

All studies explored the association between SF and OS in HBP cancers. Pooled results revealed that elevated SF was associated with poor OS (HR 1.60, 95% CI 1.36 to 1.88, p<0.001) (figure 2). A fixed effects model was employed because there was no significant heterogeneity between the studies (I^2=37.1%, p=0.146).

Subgroup analyses were conducted based on cancer type, ethnicity, TNM stage, cut-off value of SF and NOS score (table 2). High SF was associated with worse OS in patients with HBP cancers regardless of the cancer type (HCC, PC, ICC and HBC), race (Asian and Caucasian), SF cut-off value (≤250 and >250), TNM stage (III–IV and I–IV) and NOS score (≤7 and >7).

SF and RFS/PFS/TTR in HBP cancers

Four studies comprising 901 participants had data revealing the relationship between SF and RFS/PFS/TTR in HBP cancers. A random effects model was employed because of the significant heterogeneity between the studies (p=0.003, I^2=78.0%). Pooled results revealed that elevated SF was associated with worse prognosis for RFS/PFS/TTR (HR 1.70, 95% CI 1.15 to 2.52, p=0.008) (figure 3).

Sensitivity analysis

A sensitivity analysis was carried out to assess the effect of individual studies on the overall estimate (figure 4). The influence of the single data sets on the pooled HRs for OS was assessed by excluding one study at a time. No single study had a significant influence on the overall effect size. This indicated that the results were credible and stable.

Table 1 Characteristics of the studies included in the meta-analysis

Study cohort	Year	Study region	Cancer type	Patients (n)	Follow-up (months)	Treatment	Age (years)	Cut-off value	Stage (TNM/BCLC)	Outcome	HR	NOS score
Facciorusso et al[20]	2014	Italy	HCC	103	78 (68–82)	RFA	70 (39–86)	244	0–B	OS/TTR	M	7
Alkhateeb et al[27]	2014	USA	PC	159	NR	Chemotherapy	NR	840	III–IV	OS	U	5
Wang et al[19]	2015	China	PC	79	32 (3–59)	Mix	NR	330	NR	OS/PFS	U/M	7
Xun and Li[29]	2016	China	ICC	104	41 (1–92)	Mix	NR	200	I–IVb	OS	M	7
Uchino et al[21]	2018	Japan	HCC	292	NR	RFA	NR	244	NR	OS/RFS	U	7
Song et al[28]	2018	Korea	HBC	80	NR	KM	59.7	200	IV	OS	M	8
Wu et al[16]	2019	China	HCC	427	45 (2–101)	Surgery	47.5 (18–82)	267	I–IV/0–C	OS/RFS	M	9

HR is obtained by reporting in text (R). 'M' means the HR comes from multivariate analysis. 'U' means the HR comes from univariate analysis.
BCLC, Barcelona Clinic Liver Cancer; HBC, hepatobiliary cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; KM, Korean medicine; NOS, Newcastle-Ottawa Scale; NR, not reported; OS, overall survival; PC, pancreatic cancer; PFS, progression-free survival; RFA, radiofrequency ablation; RFS, recurrence-free survival; TNM, tumour-node-metastasis; TTR, time to recurrence.
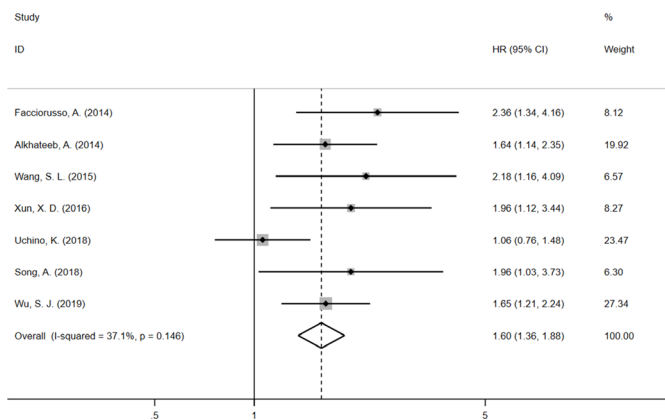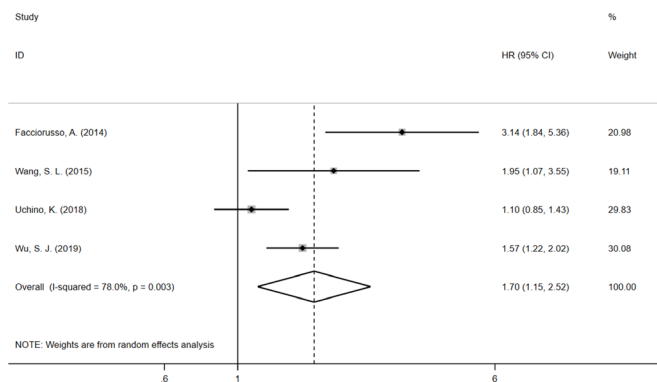
Figure 2 Meta-analysis of the association between pretreatment serum ferritin (SF) and overall survival (OS) of patients with hepatobiliary and pancreas (HBP) cancers. Results are presented as individual and pooled HRs and 95% CIs.

Figure 3 Meta-analysis of the association between serum ferritin (SF) and recurrence-free survival (RFS)/progression-free survival (PFS)/time to recurrence (TTR) of hepatobiliary and pancreas (HBP) cancers. Results are presented as individual and pooled HRs and 95% CIs.

DISCUSSION

The prognostic value of SF in HBP cancers

In recent years, the number of patients diagnosed with HBP cancers has increased all over the world.[1 2 5 30 31] The majority of the patients diagnosed with HBP cancers are usually at an advanced stage. Despite the significant improvements made in the treatment of HBP cancers, their prognosis remains dismal.[2 5 6] Precise prognostic forecast of patients with HBP cancers is critical for making further management decisions. Inflammation can result in tumour initiation, progression and dissemination. It is further related to increasing epithelial to mesenchymal transition.[32] Serum inflammatory indices, such as lymphocyte to monocyte ratio,[33–35] platelet to lymphocyte ratio and neutrophil to lymphocyte ratio,[36–39] have been found to have better prognostic value in patients with HBP cancer. Similarly, pretreatment SF is a novel inflammatory factor elevated in multiple human malignant tumours. It is associated with survival prognosis in

Table 2 Pooled HRs for OS according to subgroup analyses

Subgroup	Studies (n)	Patients (n)	Effects model	HR (95% CI)	P value	Heterogeneity	
						I² (%)	Ph
Overall	7	1244	Fixed	1.596 (1.358 to 1.876)	<0.001	37.1	0.146
Cancer type							
HCC	3	633	Random	1.53 (1.01 to 2.32)	0.043	70.9	0.032
PC	2	238	Fixed	1.76 (1.29 to 2.41)	<0.001	0	0.443
ICC	1	104	–	1.96 (1.12 to 3.44)	0.019	–	–
HBC	1	80	–	1.96 (1.03 to 3.73)	0.04	–	–
Race							
Asian	5	982	Fixed	1.52 (1.25 to 1.83)	<0.001	45.9	0.116
Caucasian	2	262	Fixed	1.82 (1.34 to 2.43)	<0.001	11.2	0.288
Cut-off value							
≤250	4	579	Random	1.68 (1.10 to 2.56)	0.016	63.2	0.043
>250	3	665	Fixed	1.70 (1.37 to 2.12)	<0.001	9	0.713
TNM stage							
III–IV	2	239	Fixed	1.71 (1.25 to 2.35)	0.001	0	0.636
I–IV	2	531	Random	1.71 (1.31 to 2.25)	<0.001	0	0.591
NOS score							
≤7	5	737	Random	1.67 (1.22 to 2.29)	0.001	55.6	0.061
>7	2	507	Fixed	1.70 (1.29 to 2.25)	<0.001	0	0.632

HBC, hepatobiliary cancer; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; NOS, Newcastle-Ottawa Scale; OS, overall survival; PC, pancreatic cancer; Ph, p values of Q test for heterogeneity test; TNM, tumour-node-metastasis.
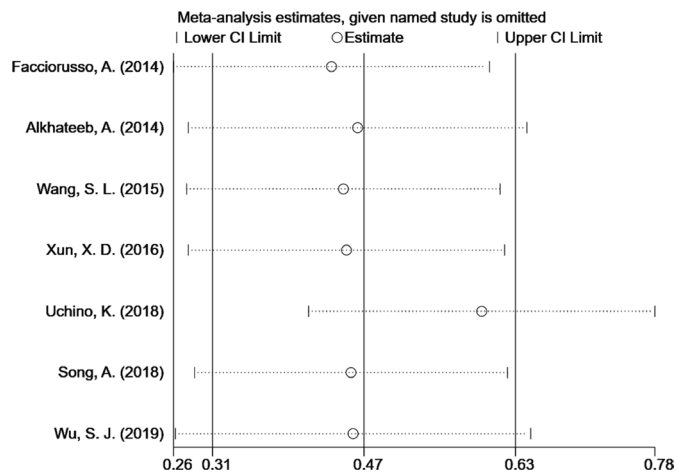
Figure 4 Chart of sensitivity analysis.

patients with HBP cancers.[16 19 28 29] Cognisant to this, SF may serve as a novel prognostic factor for patients with HBP cancer. To the authors' knowledge, this is the first meta-analysis that assesses the prognostic value of pretreatment SF in HBP cancers. So far, there is only one meta-analysis found that high SF may predict poor OS in patients with cancer (acute myeloid leukaemia and myelodysplastic syndromes).[40]

High SF predicted worse prognosis in HBP cancers

This meta-analysis combined seven studies comprising 1244 patients. Elevated pretreatment SF was associated with worse OS and RFS/PFS/TTR in patients with HBP cancers. Subgroup analysis further revealed that high SF was significantly associated with shorter OS in patients with HBP cancers regardless of cancer type, race, SF cut-off value, TNM stage and NOS score. Consequently, pretreatment SF may be considered as an available prognostic biomarker for patients with HBP cancers. These results were proved to be credible and stable based on sensitivity analysis. However, considering that the sample sizes included in this study are relatively limited, our results are in need of cautious interpretation. SF is a widely available, routinely measured and cost-effective inflammatory biomarker. Therefore, SF can be routinely tested as a clinical index before treatment in patients with HBP cancers. The levels of pretreatment SF might be used as a predictive tool for monitoring treatment response. Elevated pretreatment SF levels that indicated poor prognosis of patients with HBP cancers would help practitioners provide optimal care and management for these patients. Consequently, SF could be used as a practical reference for predicting the prognosis and adjusting the treatment strategy in patients with HBP cancers. Further studies ascertaining the biological basis of the association between pretreatment SF and survival outcome may result in uncovering new therapeutic targets for the development of innovative, biologically based adjuvant therapy for HBP cancers.

The underlying molecular mechanisms of SF related to HBP cancer prognosis

The specific molecular mechanisms involved in the prognostic effect of SF in HBP cancers remain unknown. SF plays a vital role in maintaining iron balance as one of the main storage and carrier proteins of iron. Iron plays a significant role in DNA synthesis and cell proliferation.[41] Tumour cells need more iron than normal cells because of their differences in cell regenerative capacity.[18] Besides storing iron and maintaining iron homeostasis, SF participates in immune regulation, tumour angiogenesis and proliferation.[8–10 13 20 42] SF synthesis is induced by hepatocytes and macrophages. SF has been reported to be overexpressed in tumour-associated macrophages.[8–10 18 43 44] In addition, SF can bind high molecular weight kininogen thereby inhibiting its antiangiogenic effect.[45] It is also capable of inhibiting the proliferation of haematopoietic progenitor cells and lymphocytes.[46 47] Further to this, it may play an additional role in promoting tumour cell proliferation through a non-iron-mediated mechanism.[43] To sum up, high SF levels may indicate a proinflammatory environment, antitumour immune activity and/or antitumour proliferation ability. It is thus not surprising that SF is associated with an unfavourable prognosis in patients with cancer which has again been confirmed by our meta-analysis.

The limitation of this meta-analysis

Nevertheless, this study was limited by several factors. Most of the included studies were retrospective that may have led to selection bias and thus affected the reliability of our results. However, interestingly, the sensitivity analysis indicated that our results were credible and stable. Even so, large-scale multicentre prospective cohorts are required to clarify the prognostic value of pretreatment SF in HBP cancers. In the same line, there were insufficient data to explore the relationship between pretreatment SF and clinicopathological features. Therefore, additional studies are needed to address this issue. Moreover, all the studies were published in English and thus could cause publication bias. In addition, publication bias may exist as most studies included in this meta-analysis had significant findings, which is due to the fact that journals are more likely to publish studies with significant findings. Finally, the cut-off value of SF varied among studies that might lead to heterogeneity between studies. In view of this, we conducted subgroup analyses on cut-off value of SF in this study. In the future, the optimal cut-off value of SF should be validated for further research needs and clinical application.

CONCLUSION

This study demonstrated that elevated pretreatment SF was associated with worse prognosis in patients with HBP cancers. As such, it may serve as a novel prognostic biomarker for HBP cancers. Future research which is well designed and large scale is required to clarify this conclusion.

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