Spleen plays a two-way role in cancer incidence and cancer progression

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Research Article

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Abstract

Background:

The link between splenectomy and cancer outcomes remains unclear. Our aim was to investigate the association between splenectomy and cancer incidence, cancer progression in cancer patients.

Methods:

Pooled estimates of the relative risks (RR) for cancer incidence and cancer progression were performed in a meta-analysis by random effects or fixed effects models as appropriate.

Results:

Eighty-one literatures were included in our meta-analysis. We found some interesting results. First, splenectomy was associated with a significantly increased risk of overall cancer, Non Hodgkin lymphoma, Hodgkin lymphoma, lung cancer, leukemia, breast cancer, oral and pharyngeal cancer, skin cancer, esophagus cancer, prostate cancer, bladder cancer, gastric cancer, pancreas cancer, brain and nervous system cancer. Interestingly, splenectomy for trauma increased the risk of liver cancer while splenectomy for protal hypertension decreased the risk of liver cancer. Second, splenectomy was associated with a significantly lower 5-year overall survival (OS) for gastric cancer, colorectal cancer, esophageal and esophago-gastric junction cancer while splenectomy was associated with a significantly higher 5-year OS for liver cancer. Subgroup analyses based on tumor stage showed that splenectomy for gastric cancer was associated with a significantly lower 5-year OS only for stage □ and stage □ but stage □and stage □. Third, splenectomy increased the rate of hospital mortality of gastric cancer but had no effects on the hospital mortality of liver cancer, esophageal and esophago-gastric junction cancer. Finally, splenectomy increased the incidence of some specific postoperative complications for cancer patients.

Conclusions:

Splenectomy was associated with cancer incidence, cancer survival, hospital mortality, and postoperative complications. Spleen plays a two-way role in cancer incidence and cancer progression.

1. Background

Spleen is the largest secondary lymphoid organ and plays a crucial role in the regulation of innate and adaptive immune [1]. The tumor immune microenvironment contains various immunosuppressive cells, such as myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM) and tumor-associated neutrophils (TAN), which contribute to tumor progression [2, 3]. Spleen is an important extramedullary hematopoiesis site and splenic hematopoietic stem and progenitor cells (HSPC) produce MDSC, TAM and TAN in tumor [4]. Our previous study found a large number of MDSC accumulated in the spleen and the spleen weight was positively correlated with the percentages of MDSC in the spleen of H22 hepatoma tumor-bearing mice [5]. Additionally, the spleen is also the site tumor immunetolerance occurred [6].

As such, an increasing number of studies have reported the roles of the spleen and splenectomy in tumor behavior. As for cancer incidence, Kristinsson and colleagues reported patients undergoing splenectomy for external trauma increased the risk of cancer while Linet and colleagues reported patients undergoing

splenectomy for external trauma had no significant excess of total or site-specific cancers [7, 8]. Interestingly, patients undergoing splenectomy for post-hepatitis cirrhosis reduced risk of hepatocellular carcinoma [9]. Animal study indicated spleen plays a major role in a genetic mouse model of Notch ligand delta like 4 (DLL4)-driven T-cell acute lymphoblastic leukemia [10]. However, to the best of our knowledge, there is no consensus on the role of splenectomy in tumor progression. Animal study indicated that the role of splenectomy in the progression of non-small cell lung cancer depended on the time of splenectomy performed [11]. Our previous study indicated that splenectomy could reduce the percentage of MDSC and inhibit hepatocellular carcinoma growth [12]. These different results of animal study may be caused by different tumor models or different time points of splenectomy.

The existing meta-analysis only investigated the role of splenectomy in the treatment of hepatocellular carcinoma and gastric carcinoma, and their results were also inconsistent [13–16]. The role of splenectomy in cancer progression were inconsistent in present studies may be caused by the considerable heterogeneity among studies. For example, the reasons for splenectomy included trauma, hypersplenism, immune thrombocytopenia, iatrogenic injury and so on. The existing meta-analysis did not investigate the role of splenectomy in cancer incidence.

The objective of this study was to investigate the role of splenectomy in cancer incidence and cancer progression by meta-analysis incorporating results from more recently published studies. In our study we also investigated the role of splenectomy in cancer incidence and the progression of hepatocellular carcinoma, gastric carcinoma, colorectal cancer, esophageal cancer and esophago-gastric junction cancer. In addition, we included reasons of splenectomy, tumor stage, study design and surgical method of gastrectomy in the subgroup analysis.

2. Materials And Methods

2.1 Inclusion and exclusion criteria

We chose published studies regarding the following inclusion criteria: (1) prospective randomized controlled trials (RCT) or non-randomized controlled trials (nRCT) that compared the safety and long-term oncological outcomes of splenectomy to those of non-splenectomy with accessible full texts; (2) providing sufficient data for outcomes evaluation, including cancer development, overall survival (OS), mortality, and/or complication; (3) the study group were splenectomy; (4) studies published in English language before August 7, 2021. Studies were excluded if they met the following criteria: (1) letters, case reports, reviews, meta-analysis, animal studies or in vitro studies; (2) overlapping data or repeat subjects; (3) studies did not provide sufficient outcome data; (4) patients with remnant gastric cancer; (5) studies published in any language other than English. At least two reviewers (YJ, LY, JW) independently performed study selection according to inclusion and exclusion criteria, with discrepancies resolved by consensus.

2.2 Search strategy

A systematic literature search was conducted by two of the authors (YJ and JW) through the Pub Med, Embase and Web of Science. Literature searches were updated on August 7, 2021 and restricted to English written full-text articles. The following search terms were used: (“splenectomy”) AND (“cancer” OR “carcinoma” OR “malignancy” OR “neoplasm” OR “neoplasin” OR “tumor” OR “tumour” OR “cirrhosis” OR “hypersplenism” OR “portalhypertension”). The references of the included articles, meta-analysis articles and reviews were also

searched. This meta-analysis was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [17].

2.3 Quality assessment

The quality of RCT was evaluated using the Cochrane risk of bias tool. Seven items were evaluated for quality assessment: (1) whether the method of allocation was truly random; (2) whether there was allocation concealment; (3) whether there was equality between the two groups at baseline prognostic characteristics; (4) whether the eligible inclusion/exclusion criteria were described; (5) whether blinding assessment was performed; (6) whether loss to followup in each treatment arm was demonstrated; (7) whether intentiontotreat analysis was considered. Trials including 7 or 6 items to be rated as high quality, those with 5 or 4 items to be rated as fair quality, and those including less than 3 items to be rated as low quality [18]. The quality of other studies was assessed using the Newcastle–Ottawa Scale (NOS). Eight items across three domains were evaluated for quality assessment: selection (four items, one star each), comparability (one item, up to two stars), and exposure (three items, one star each) [19]. Studies including at least 7 stars to be rated as good, those at lest 4 stars to be rated as fair, and those including less than 3 stars to be rated as poor.

2.4 Data extraction and data analysis

Two reviewers (YJ and LZ) independently extracted data (first author's name, year of publication, country, participant number, age, gender, cancer types, reasons of splenectomy, tumor stage, study design, surgical method of gastrectomy, Child-Pugh classification, 5-year overall survival (OS), complication, mortality, and association strength of tumorigenesis with corresponding 95% confidence intervals (CI) and discussed any discordance to reach agreement. If other statistics were reported instead of strength of tumorigenesis with corresponding 95% CI, we requested the data from the corresponding author via e-mail.

2.5 Statistical analysis

Stata 14.0 (StataCorp LP, College Station, TX, USA) was used for all analyses. Meta-analyses were performed if the number of studies was equal to or exceeded two. These meta-analyses were based on random effects model if heterogeneity is significant while fixed effects model was used if heterogeneity is not significant. Relative risks (RR) and 95% CI were used to assess the effect size. The comparative groups were individuals with splenectomy versus the no splenectomy group. If the RR was not reported, we assumed odds ratio (OR) or hazard ratio (HR) could be considered approximatively equivalent to the RR. The significance level was defined as $P < 0.05$.

The Q test and I^2 statistic were used to evaluate heterogeneity between studies. An $I^2 \geq 50\%$ was considered high heterogeneity and we pooled the results using a random-effects model. In order to resolve heterogeneity, subgroups analyses were performed based on reasons of splenectomy (trauma, protal hypertension, and other no trauma), tumor stage (Ⅰ, Ⅱ, Ⅲ, Ⅳ), study design (RCT and nRCT), surgical method of gastrectomy (total gastrectomy and no total gastrectomy) and surgical method of splenectomy (splenectomy and pancreaticosplenectomy). Publication bias was examined using Egger´s test if the number of studies was more than five. $P < 0.05$ was considered the presence of small-study effect.

3. Results

3.1 Search results

A total of 13918 literatures were searched and 6431 articles were excluded because of duplicate results. Among the remaining 7487 records, 7362 were excluded through title or abstract screening, leaving 125 records for further full-text screening. Finally, 81 literatures were included in our meta-analysis (Figure S1). Three studies assessed two outcomes resulting in a total of 84 reports [7, 20, 21]. Of these, 7 studies reported the incidence risk for all sites combined or site-specific cancer [7-9, 20-23], 50 studies examined the impact of splenetomy on the progression of gastric carcinoma [24-73], 4 studies investigated the role of splenetomy in the progression of colorectal cancer [74-77], 6 studies examined the impact of splenetomy on the progression of esophago-gastric junction cancer [78-83], and 14 studies examined the impact of splenetomy on the progression of hepatocellular carcinoma [84-97]. Among 50 studies for gastric carcinoma contained 7 RCTs [30, 32, 42, 48, 50, 52, 68]. The detailed study characteristics and the quality of studies are shown in Table S1-S6.

3.2 Associations between splenectomy and the risk of cancer incidence

The meta-analysis results of 8 reports showed that splenectomy was associated with a significantly increased risk of overall cancer incidence from random-effects model (RR: 1.476, 95% CI: 1.182–1.843; Table 1, Figure S2), with a high heterogeneity (I^2= 89.6%, P < 0.001). Similarly, splenectomy also increased the incidence risk of Non Hodgkin lymphoma (NHL, RR: 3.867, 95% CI: 2.055–7.277; I^2= 71.4%; Table 1, Figure S3) and Hodgkin lymphoma (HL, RR: 6.714, 95% CI: 1.502–30.003; I^2= 65.9%; Table 1, Figure S4) with high heterogeneity. For other specific cancers, significant associations were observed in lung cancer (RR: 1.28, 95% CI: 1.145–1.440; I^2= 15.0%; Table 1, Figure S5), leukemia (RR: 5.376, 95% CI: 4.431–6.523; I^2= 34.1%; Table 1, Figure S6), breast cancer (RR: 1.574, 95% CI: 1.105–2.242; I^2= 0%; Table 1, Figure S7), oral and pharyngeal cancer (RR: 1.285, 95% CI: 1.034–1.598; I^2= 0%; Table 1, Figure S8), skin cancer (RR: 1.760, 95% CI: 1.004–13.088; I^2= 0%; Table 1, Figure S9), esophagus cancer (RR: 2.058, 95% CI: 1.529–2.770; I^2= 41.7%; Table 1, Figure S10), prostate cancer (RR: 1.253, 95% CI: 1.070–1.467; I^2= 6.0%; Table 1, Figure S11), bladder cancer (RR: 1.300, 95% CI: 1.005–1.683; I^2= 0%; Table 1, Figure S12), gastric cancer (RR: 1.920, 95% CI: 1.394–2.643; I^2= 30.2%; Table 1, Figure S13), pancreas cancer (RR: 1.779, 95% CI: 1.228–2.577; I^2= 0%; Table 1, Figure S14), and brain and nervous system cancer (RR: 3.941, 95% CI: 1.080–14.380; I^2= 0%; Table 1, Figure S15) with low heterogeneity. However, splenectomy had no effect on the incidence risk of liver cancer (RR: 1.436, 95% CI: 0.469–4.397; I^2= 97.7%; Table 1, Figure S16), colorectal cancer (RR: 1.152, 95% CI: 0.919–1.444; I^2= 14.9%; Table 1, Figure S17), and kidney cancer (RR: 1.121, 95% CI: 0.724–1.736; I^2= 15.2%; Table 1, Figure S18). Furthermore, there was no publication bias among included studies as demonstrated by Egger´s test (Table 1).

The reasons of splenectomy included trauma and no trauma, such as hypersplenism, benign hematologic disorders, and other no trauma reasons. Subgroups analyses were performed where there were three or more studies based on reasons of splenectomy (trauma, protal hypertension, and other no trauma). Interestingly, subgroup analyses based on reasons of splenectomy showed that splenectomy for trauma increased the incidence risk of liver cancer (RR: 2.068, 95% CI: 1.525–2.805; I^2= 0%; Table 2, Figure S16) while splenectomy for protal hypertension decreased the incidence risk of liver cancer (RR: 0.524, 95% CI: 0.423–0.649; I^2= 0%; Table 2, Figure S16) with low heterogeneity. Our results from subgroup analyses also found only splenectomy for no trauma reasons increased the incidence risk of breast cancer (RR: 1.639, 95% CI: 1.046–2.568; I^2= 0%; Table 2, Figure S7) and skin cancer (RR: 1.915, 95% CI: 1.020–3.596; I^2= 0%; Table 2, Figure S9) while only splenectomy for trauma increased the incidence risk of oral and pharyngeal cancer (RR: 1.265, 95% CI: 1.011–1.583; I^2= 0%;

Table 2, Figure S8) and prostate cancer (RR: 1.236, 95% CI: 1.052–1.460; I^2= 0%; Table 2, Figure S11). The results of incidence risk of bladder cancer changed from significant to non-significant in subgroup analyses (Table 2, Figure S12). The results of subgroup analyses on reasons of splenectomy for the incidence of all cancer, NHL, lung cancer, leukemia, esophagus cancer, gastric cancer, pancreas cancer, and colorectal cancer were consistent with the main effect and subgroup analyses partially or completely resolved heterogeneity (Table 2, Figure S2, S3, S5, S6, S10, S13, S15, S17).

3.3 Associations between splenectomy and the 5-year OS of cancer patients

We next investigated the associations between splenectomy and the 5-year OS of gastric cancer, liver cancer, colorectal cancer, and esophageal and esophago-gastric junction cancer. The meta-analysis results of 39 reports showed that splenectomy was associated with a significantly lower 5-year OS of gastric cancer based on a random-effects model (RR: 0.787, 95% CI: 0.734–0.844; Table 3, Figure S19), with a high heterogeneity (I^2= 60.1%, P < 0.001). Similarly, splenectomy was also associated with a significantly lower 5-year OS of colorectal cancer (RR: 0.769, 95% CI: 0.555–0.859; I^2= 0%; Table 3, Figure S20), esophageal and esophago-gastric junction cancer (RR: 0.541, 95% CI: 0.397–0.737; I^2= 34.8%; Table 3, Figure S21) based on a fixed-effects model. Interestingly, the meta-analysis results of 10 reports showed that splenectomy was associated with a significantly higher 5-year OS of liver cancer based on a fixed-effects model (RR: 1.173, 95% CI: 1.076–1.279; Table 3, Figure S22), with a low heterogeneity (I^2= 39.7%, P = 0.093). Similarly, there was also no publication bias among included studies as demonstrated by Egger´s test (Table 3).

Subgroups analyses were performed for gastric cancer based on study design (RCT and nRCT), surgical method of gastrectomy (total gastrectomy), surgical method of splenectomy (splenectomy and pancreaticosplenectomy), and tumor stage (□, □, □, □). Our results indicated that the patients underwent splenectomy had lower 5-year OS only in nRCT (RR: 0.760, 95% CI: 0.712–0.810; I^2= 43.2%; Table 4, Figure S19) but RCT (RR: 0.988, 95% CI: 0.882–1.108; I^2=23.5%; Table 4, Figure S19). Surgical methods of gastrectomy and splenectomy did not affect the 5-year OS of gastric cancer (Table 4). Interestingly, we found only stage □ (RR: 0.821, 95% CI: 0.707–0.953; I^2= 0%; Table 4, Figure S23) and stage □ (RR: 0.723, 95% CI: 0.618–0.846; I^2= 0%; Table 4, Figure S23) gastric cancer patients underwent splenectomy had lower 5-year OS but stage □ (RR: 0.936, 95% CI: 0.839–1.044; I^2= 0%; Table 4, Figure S23) and stage □ (RR: 1.048, 95% CI: 0.545–2.014; I^2= 29.4%; Table 4, Figure S23).

3.4 Associations between splenectomy and the hospital mortality of cancer patients

There were 26 studies reported the hospital mortality of gastric cancer patients after splenectomy, 9 studies for liver cancer, and 5 studies for esophageal and esophago-gastric junction cancer. As shown in the results of meta-analysis, gastric cancer patients in splenectomy group showed a significantly higher hospital mortality based on a fixed-effects model, with a low heterogeneity (RR: 1.461, 95% CI: 1.229–1.736; I^2= 47.2%; Table 5, Figure S24). There were no significant differences in hospital mortality for liver cancer (RR: 1.572, 95% CI: 0.757–3.080; I^2= 0%; Table 5, Figure S25) and esophageal and esophago-gastric junction cancer (RR: 1.658, 95% CI: 0.948–2.900; I^2= 47.7%; Table 5, Figure S26). There was also no publication bias among included studies as demonstrated by Egger´s test (Table 5).

Similarly, subgroups analyses were performed for gastric cancer based on study design (RCT and nRCT), surgical method of gastrectomy (total gastrectomy), and surgical method of splenectomy (splenectomy and

pancreaticosplenectomy). Our results indicated that there were no significant differences in hospital mortality for gastric cancer who underwent total gastrectomy with a low heterogeneity (RR: 0.906, 95% CI: 0.544–1.508; I^2= 0%, Table 6, Figure S27). Study design and surgical methods of splenectomy did not affect the hospital mortality of gastric cancer (Table S7).

3.5 Associations between splenectomy and the complications after surgery

There were 35 studies yielded a pooled RR of 1.818 (95% CI: 1.523–2.171; Table 6) for the association between the total postoperative complications of gastric cancer patients and splenectomy based on random-effects model analyses. High heterogeneity was observed with I^2 = 80.7%. Regarding to specific postoperative complication, our result showed that splenectomy group had higher incidence of anastomotic leakage (RR: 1.853, 95% CI: 1.501–2.288; I^2= 0%, Table 6), pulmonary complication (RR: 1.584, 95% CI: 1.257–1.996; I^2= 0%, Table 6), intraabdominal abscess (RR: 2.914, 95% CI: 1.672–5.081; I^2= 67.2%, Table 6), pancreatic fistula (RR: 5.390, 95% CI: 2.571–11.298; I^2= 73.3%, Table 6), and wound infection (RR: 1.461, 95% CI: 1.023–2.088; I^2= 0%, Table 6). There was no significant difference between two groups in the incidence of ileus, postoperative bleeding, cardiac complication, liver dysfunction, pancreatits, anastomotic stenosis, renal dysfunction, and sepsis (Table 6). The results of Egger ´s test showed there was publication bias in the analysis of total postoperative complications and liver dysfunction.

Our results showed that the splenectomy for liver cancer did not increase the total postoperative complication rate (RR: 1.124, 95% CI: 0.949–1.331; Table 7) based on fixed-effects model analyses, with a low heterogeneity between studies (I^2= 15.7%). Regarding to specific postoperative complication, we found splenectomy for liver cancer increased the incidence of postoperative bleeding (RR: 2.230, 95% CI: 1.077–4.617; I^2= 0%, Table 7) and portal vein or splenic vein thrombosis (PSVT; RR: 23.912, 95% CI: 6.782–80.306; I^2= 21.6%, Table 7) with a low heterogeneity based on fixed-effects model analyses. There was no significant difference between two groups in the incidence of pleural effusion, bile leakage, ascites, wound infection, upper gastrointestinal haemorrhage, pulmonary infection, and liver failure (Table 7). As showed in Table 8, splenectomy for esophageal and esophago-gastric junction cancer increased the incidence of leakage (RR: 1.935, 95% CI: 1.116–3.355; I^2= 72.3%, Table 8) with a high heterogeneity based on random-effects model analyses. There was no significant difference between two groups in the incidence of pulmonary complications, cardiac complications, wound infection, and postoperative bleeding (Table 8).

4. Discussion

The present meta-analysis confirms that splenectomy was associated with cancer incidence, cancer survival, hospital mortality, and postoperative complications. Our study also found some interesting results. First, splenectomy was associated with a significantly increased incidence risk of overall cancer, Non Hodgkin lymphoma, Hodgkin lymphoma, lung cancer, leukemia, breast cancer, oral and pharyngeal cancer, skin cancer, esophagus cancer, prostate cancer, bladder cancer, gastric cancer, pancreas cancer, and brain and nervous system cancer but had no effect on the incidence risk of colorectal cancer and kidney cancer. Interestingly, subgroup analyses based on reasons of splenectomy showed that splenectomy for trauma increased the incidence risk of liver cancer while splenectomy for protal hypertension decreased the incidence risk of liver cancer. Second, splenectomy was associated with a significantly lower 5-year OS for gastric cancer, colorectal cancer, esophageal and esophago-gastric junction cancer while splenectomy was associated with a significantly

higher 5-year OS for liver cancer. Subgroup analyses based on tumor stage showed that splenectomy for gastric cancer was associated with a significantly lower 5-year OS only for stage □ and stage □ but stage □and stage □. Third, splenectomy increased the rate of hospital mortality of gastric cancer patients but had no effects on the hospital mortality of liver cancer patients, esophageal and esophago-gastric junction cancer patients. Finally, splenectomy increased the incidence of some specific postoperative complications for gastric cancer, liver cancer, esophageal and esophago-gastric junction cancer.

Spleen is the largest secondary lymphoid organ and plays a crucial role in immunologic defenses, cancer incidence and cancer progression [98, 99]. Mouse model has suggested that splenectomy is associated with increased colon cancer induction [100]. The common reasons of splenectomy are trauma, protal hypertension, benign hematologic disorders and other no trauma reasons. But the role of splenectomy in cancer incidence still remains unclear. An epidemiological study based on 8149 cancer-free splenectomized patients (average follow-up 12.6 years) found a 50% increased risk of solid and hematologic malignancies incidence [8]. A cohort study consisted of including 2603 patients with nontraumatic and 2295 patients with traumatic splenectomy, found both nontraumatic and traumatic splenectomy had a significantly higher risk for overall cancer, certain gastrointestinal tract cancers, head and neck cancers, hematological malignancies development [21]. On the other hand, a study based on 1103 splenectomized patients for traumatic reason (average follow-up 6.8 years) found no cancer incidence increased, however, an increased risk for some specific cancer was found among 5212 patients who underwent splenectomy for non-traumatic reasons [20]. Similarly, another study based on 1295 splenectomized patients for traumatic reason showed no cancer incidence increased, while 985 patients who splenectomy accompanied surgical treatment of non-malignant conditions of adjacent organs with significant increases of lung and ovarian cancers [7]. Splenectomy affects cancer incidence may through impairing immune surveillance in the host. Our results found splenectomy was associated with a significantly increased incidence risk of overall cancer. For specific cancers, splenectomy increased incidence risk of overall cancer, Non Hodgkin lymphoma, Hodgkin lymphoma, lung cancer, leukemia, breast cancer, oral and pharyngeal cancer, skin cancer, esophagus cancer, prostate cancer, bladder cancer, gastric cancer, pancreas cancer, and brain and nervous system cancer but had no effect on the incidence risk of colorectal cancer and kidney cancer. Splenectomized patients for trauma increased the incidence risk of oral and pharyngeal cancer and prostate cancer, while splenectomy for no trauma reasons increased the incidence risk of breast cancer and skin cancer. Our study supports the opinion that splenectomy should be performed more conservatively in medical practice in the future. The effect and exact mechanism of splenectomy promotes cancer incidence is exceedingly complex and not clear yet. These results indicated that spleen plays a two-way role in cancer incidence. More epidemiological study needed to clear the role of splenectomy in cancer incidence and more basic study needed to elucidate the mechanism of splenectomy promotes cancer incidence.

Liver cancer is a consequence of hepatitis and liver cirrhosis [101]. Portal hypertension and subsequent hypersplenism is also the result of liver cirrhosis. Portal hypertension is characterized by anemia, leucopenia, thrombocytopenia and splenomegaly. Our previous studies found the immune function of spleen from patients with portal hypertension changed significantly. We found the lymphocyte density in the spleen decreased but the total quantity of lymphocytes increased in patients with portal hypertension [102]. We also found macrophages in the spleen of portal hypertension patients were hyperactivated and secreting both pro-inflammatory and pro-fibrogenic factors such as interleukin-1β (IL-1β), interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α) and TGF-β1 [103, 104]. Liver stem cells are involved in hepatocarcinogenesis after liver cirrhosis and our study found splenic serum from portal hypertensive patients enhances liver stem cell proliferation and self-renewal via the IGF-II/ERK

signaling pathway [105]. However, hypersplenism secondary to liver cirrhosis and portal hypertension is a strong risk factor for liver cancer incidence and splenectomy is an effective treatment of hypersplenism [9, 106]. Studies from our group have shown that splenectomy reduced liver inflammation and fibrosis severity by reducing monocyte/macrophage infiltration within the liver and promoting the phenotypic switch of infiltrating macrophages to a $Ly6C^{low}$ phenotype [107, 108]. Splenectomy also complete remitted of hypersplenism and improved liver function [9]. Our group also indicated splenectomy also evidently improved anti-tumor immune in patients with portal hypertension. Cirrhotic patients with portal hypertension showed increased proportions of CD8 and NK cells, decreased proportion of regulatory T cells (Tregs) cells, decreased expression of PD-1 in peripheral blood CD4/8 T cells, and changed in 28 cytokines which involved in cellular processes, responses to stimuli, immune processes, and pathways in cancer after splenectomy [109, 110]. Our group also study has also suggested splenectomy as a supplemental treatment for anti-HCV therapy in combination with pharmaceuticals [111]. These studies indicated that splenectomy may reduce the incidence of liver cancer risk of patients with portal hypertension and hypersplenism. In this study we found that splenectomy for trauma increased the incidence risk of liver cancer while splenectomy for protal hypertension decreased the incidence risk of liver cancer.

Our present study found splenectomy was associated with a significantly lower 5-year OS for gastric cancer, colorectal cancer, esophageal and esophago-gastric junction cancer while splenectomy was associated with a significantly higher 5-year OS for liver cancer. This interesting finding may be explained by the following reasons. First the reasons for splenectomy in patients with different types of cancer are different in medical practice. The main reason for splenectomy in gastric cancer patients was to dissection of splenic hilar lymph nodes [52]. Incidental splenectomy for iatrogenic splenic injury during operation is an infrequent but well recognized adverse event in colorectal cancer and esophageal cancer patients [77, 82]. However, synchronous splenectomy and hepatectomy has been suggested for the treatment of liver cancer and secondary hypersplenism [96]. Second, iatrogenic splenectomy may result in serious immunological consequences as the spleen is the largest secondary lymphoid organ [98]. Third, the tissue structure and immune function of the spleen have changed because of portal hypertension. Splenectomy for liver cancer patients could increase the counts of hemocytes, ameliorate liver function, facilitate liver regeneration, reduce portal venous pressure, and improve immune functions [87, 112, 113]. Finally, splenectomy could decrease the portal flow and reduce the unfortunate episode of variceal bleeding, which could increase the 5-year OS [16].

Our previous study found that the percentages of Tregs and MDSC increased while the percentages of natural killer T (NKT) cells, $CD3^+CD4^+$ T cells, and $CD3^+CD8^+$ T cells decreased in the spleen of tumor bearing mice [114, 115]. Higashijima et al. reported that splenectomy could enhance tumor growth, while Imai et al. found that splenectomy had no effect on tumor growth [116, 117]. Our previous study and other studies indicated that splenectomy inhibited tumor growth [3, 12, 118]. However, Levy et al. reported that splenectomy reduced tumor growth and the development of lung metastases in a stage dependent manner [11]. These results indicated that spleen plays a two-way role in cancer progression. Our subgroup analyses based on tumor stage showed that splenectomy for gastric cancer was associated with a significantly lower 5-year OS only for stage □ and stage □ but stage □and stage □.

Previous meta-analysis found splenectomy did not increase the mortality of gastric cancer and liver cancer [13, 14, 16, 119–124]. Similarly, our study found there were no significant differences in hospital mortality for liver cancer and esophageal and esophago-gastric junction cancer between two groups. Our study found gastric

cancer patients in splenectomy group showed a significantly higher hospital mortality than no splenectomy group because our research including more studies. Regarding to postoperative complication, most meta-analysis demonstrated that gastrectomy with splenectomy had significantly higher incidence of postoperative complications, which was consistent with our results [13, 14, 119, 123, 124]. Previous meta-analysis found that the incidence rate of postoperative complications, including PSVT and pancreatic injury, was significantly higher in the splenectomy group [15]. However, We found splenectomy for liver cancer increased the incidence of postoperative bleeding and PSVT. Moreover, our study is the first time to report that splenectomy for esophageal and esophago-gastric junction cancer increased the incidence of leakage.

5 Conclusions

The present meta-analysis confirms that splenectomy was associated with cancer incidence, cancer survival, hospital mortality, and postoperative complications. Spleen plays a two-way role in cancer incidence and cancer progression.

Abbreviations

relative risks, RR

overall survival, OS

myeloid-derived suppressor cells, MDSC

tumor-associated macrophages, TAM

tumor-associated neutrophils, TAN

randomized controlled trials, RCT

confidence intervals, CI

portal vein or splenic vein thrombosis, PSVT

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no conflict of interest.

Founding

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Author Contributions

Conceived and designed the experiments: Jiang Wei and Li Zongfang. Literature searches, record screening and evaluation: Yang Juanjuan, Li Yu, Li Zongfang and Jiang Wei. Meta-analysis: Yang Juanjuan, Li Yu and Jiang Wei. Wrote the paper: Yang Juanjuan and Jiang Wei.

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References

1. Bronte, V. and M.J. Pittet, *The spleen in local and systemic regulation of immunity.* Immunity, 2013. **39**(5): p. 806-18.
2. Kumar, V., et al., *The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment.* Trends Immunol, 2016. **37**(3): p. 208-220.
3. Jiang, W., et al., *Chronic restraint stress promotes hepatocellular carcinoma growth by mobilizing splenic myeloid cells through activating beta-adrenergic signaling.* Brain Behav Immun, 2019. **80**: p. 825-838.
4. Cortez-Retamozo, V., et al., *Origins of tumor-associated macrophages and neutrophils.* Proc Natl Acad Sci U S A, 2012. **109**(7): p. 2491-6.
5. Jiang, W., et al., *Association between cellular immune response and spleen weight in mice with hepatocellular carcinoma.* Oncol Lett, 2021. **22**(2): p. 625.
6. Ugel, S., et al., *Immune Tolerance to Tumor Antigens Occurs in a Specialized Environment of the Spleen.* Cell Reports, 2012. **2**(3): p. 628-639.
7. Linet, M.S., et al., *Risk of cancer following splenectomy.* Int J Cancer, 1996. **66**(5): p. 611-6.
8. Kristinsson, S.Y., et al., *Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up.* Haematologica, 2014. **99**(2): p. 392-8.
9. Lv, X., et al., *Hypersplenism is correlated with increased risk of hepatocellular carcinoma in patients with post-hepatitis cirrhosis.* Tumor Biology, 2016. **37**(7): p. 8889-8900.
10. Xiong, H., et al., *Spleen plays a major role in DLL4-driven acute T-cell lymphoblastic leukemia.* Theranostics, 2021. **11**(4): p. 1594-1608.
11. Levy, L., et al., *Splenectomy inhibits non-small cell lung cancer growth by modulating anti-tumor adaptive and innate immune response.* Oncoimmunology, 2015. **4**(4): p. e998469.

12. Jiang, W., et al., *Spleen contributes to restraint stress induced hepatocellular carcinoma progression.* Int Immunopharmacol, 2020. **83**: p. 106420.
13. Yang, K., et al., *The Survival Benefit and Safety of Splenectomy for Gastric Cancer With Total Gastrectomy: Updated Results.* Front Oncol, 2020. **10**: p. 568872.
14. Li, Z., et al., *Systematic review and meta-analysis of splenectomy in gastrectomy for gastric carcinoma.* Int J Surg, 2019. **68**: p. 104-113.
15. Shi, X.B., et al., *Does splenectomy significantly improve the prognosis of hepatocellular carcinoma patients with hypersplenism? A systematic review and meta-analysis.* Ann Transl Med, 2021. **9**(8): p. 641.
16. Kong, J., S. Shen, and W. Wang, *Synchronous hepatectomy and splenectomy vs hepatectomy for selected patients with hepatocellular carcinoma and clinically significant portal hypertension: A systematic review and meta-analysis.* J Surg Oncol, 2019. **119**(7): p. 964-973.
17. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* BMJ, 2009. **339**: p. b2535.
18. Dissemination, N.C.f.R.a., *Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews (Report No 4)*. Vol. 2nd ed. 2001, York: NHS CRD.
19. Stang, A., *Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.* Eur J Epidemiol, 2010. **25**(9): p. 603-5.
20. Mellemkjoer, L., et al., *Cancer risk after splenectomy.* Cancer, 1995. **75**(2): p. 577-83.
21. Sun, L.M., et al., *Splenectomy and increased subsequent cancer risk: a nationwide population-based cohort study.* Am J Surg, 2015. **210**(2): p. 243-51.
22. Thai, L.H., et al., *Long-term complications of splenectomy in adult immune thrombocytopenia.* Medicine (United States), 2016. **95**(48): p. e5098.
23. Zhang, X.F. and Y. Lv, *Splenectomy may decrease the risk of hepatocellular carcinoma in patients with liver cirrhosis: A multi-institutional case-control study.* HPB, 2018. **20**: p. S372.
24. Kishimoto, H. and S. Koga, *Evaluation of gastrectomy combined with the resection of other organs in the treatment of gastric cancer.* Japanese Journal of Surgery, 1979. **9**(3): p. 173-179.
25. Sugimachi, K., et al., *Critical evaluation of prophylactic splenectomy in total gastrectomy for the stomach cancer.* Gan, 1980. **71**(5): p. 704-9.
26. Miwa, H. and K. Orita, *Splenectomy combined with gastrectomy and immunotherapy for advanced gastric cancer.* Acta Med Okayama, 1983. **37**(3): p. 251-8.
27. Suehiro, S., et al., *The negative effect of splenectomy on the prognosis of gastric cancer.* Am J Surg, 1984. **148**(5): p. 645-8.
28. Lersch, C., et al., *Monitoring immunocompetent cells in the peripheral blood of stomach cancer patients after splenectomy and gastrectomy.* J Cancer Res Clin Oncol, 1985. **110**(3): p. 225-9.
29. Brady, M.S., et al., *Effect of splenectomy on morbidity and survival following curative gastrectomy for carcinoma.* Arch Surg, 1991. **126**(3): p. 359-64.
30. Bonenkamp, J.J., et al., *Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients.* Lancet, 1995. **345**(8952): p. 745-8.
31. Griffith, J.P., et al., *Preservation of the spleen improves survival after radical surgery for gastric cancer.* Gut, 1995. **36**(5): p. 684-690.

32. Cuschieri, A., et al., *Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: Preliminary results of the MRC randomised controlled surgical trial.* Lancet, 1996. **347**(9007): p. 995-999.
33. Otsuji, E., et al., *End results of simultaneous splenectomy in patients undergoing total gastrectomy for gastric carcinoma.* Surgery, 1996. **120**(1): p. 40-4.
34. Kodera, Y., et al., *Lack of benefit of combined pancreaticosplenectomy in D2 resection for proximal-third gastric carcinoma.* World Journal of Surgery, 1997. **21**(6): p. 622-628.
35. Kwon, S.J., *Prognostic impact of splenectomy on gastric cancer: results of the Korean Gastric Cancer Study Group.* World J Surg, 1997. **21**(8): p. 837-44.
36. Wanebo, H.J., et al., *Role of splenectomy in gastric cancer surgery: adverse effect of elective splenectomy on longterm survival.* J Am Coll Surg, 1997. **185**(2): p. 177-84.
37. Otsuji, E., et al., *Total gastrectomy with simultaneous pancreaticosplenectomy or splenectomy in patients with advanced gastric carcinoma.* Br J Cancer, 1999. **79**(11-12): p. 1789-93.
38. Saji, S., et al., *Impact of splenectomy and immunochemotherapy on survival following gastrectomy for carcinoma: Covariate interaction with immunosuppressive acidic protein, a serum marker for the host immune system.* Surgery Today, 1999. **29**(6): p. 504-510.
39. Kasakura, Y., et al., *Is there a benefit of pancreaticosplenectomy with gastrectomy for advanced gastric cancer?* American Journal of Surgery, 2000. **179**(3): p. 237-242.
40. Lee, K.Y., et al., *Impact of splenectomy for lymph node dissection on long-term surgical outcome in gastric cancer.* Ann Surg Oncol, 2001. **8**(5): p. 402-6.
41. Takeuchi, K., et al., *Total gastrectomy with distal pancreatectomy and splenectomy for advanced gastric cancer.* J Surg Res, 2001. **101**(2): p. 196-201.
42. Csendes, A., et al., *A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma.* Surgery, 2002. **131**(4): p. 401-7.
43. Lo, S.S., et al., *Higher morbidity and mortality after combined total gastrectomy and pancreaticosplenectomy for gastric cancer.* World J Surg, 2002. **26**(6): p. 678-82.
44. Qin, H. and C. Lin, *Radical resection of gastric carcinoma with pancreas and spleen preservation and functional cleaning of lymph nodes.* Chin Med J (Engl), 2002. **115**(5): p. 736-9.
45. Erturk, S., et al., *Effect of simultaneous splenectomy on the survival of patients undergoing curative gastrectomy for proximal gastric carcinoma.* Surg Today, 2003. **33**(4): p. 254-8.
46. Fatouros, M., et al., *Impact of spleen preservation in patients with gastric cancer.* Anticancer Research, 2005. **25**(4): p. 3023-3030.
47. Gorbunov, E.A., et al., *Significant prognostic factors in 283 patients after surgery for adenocarcinoma of the stomach.* Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae, 2005. **78**: p. 3-16.
48. Kodera, Y., et al., *Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer.* Br J Surg, 2005. **92**(9): p. 1103-9.
49. Toneri, M., et al., *Prognosis of patients with gastric carcinoma treated in remote island hospitals in Japan: a multivariable analysis.* Anticancer Res, 2006. **26**(5b): p. 3621-5.
50. Yu, W., G.S. Choi, and H.Y. Chung, *Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer.* Br J Surg, 2006. **93**(5): p. 559-63.

51. Zhang, C.H., et al., *Spleen preservation in radical surgery for gastric cardia cancer.* Annals of Surgical Oncology, 2007. **14**(4): p. 1312-1319.
52. Yonemura, Y., et al., *Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer.* Int J Clin Oncol, 2008. **13**(2): p. 132-7.
53. Huang, C.M., et al., *Prognostic impact of splenectomy on advanced proximal gastric cancer with No. 10 lymph node metastasis.* Chin Med J (Engl), 2009. **122**(22): p. 2757-62.
54. Li, C., et al., *Lymph node dissection around the splenic artery and hilum in advanced middle third gastric carcinoma.* European Journal of Surgical Oncology, 2009. **35**(7): p. 709-714.
55. Oh, S.J., et al., *The effect of spleen-preserving lymphadenectomy on surgical outcomes of locally advanced proximal gastric cancer.* Journal of Surgical Oncology, 2009. **99**(5): p. 275-280.
56. Sasada, S., et al., *Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer.* Anticancer Res, 2009. **29**(8): p. 3347-51.
57. Verlato, G., et al., *Indexes of surgical quality in gastric cancer surgery: experience of an Italian network.* Ann Surg Oncol, 2009. **16**(3): p. 594-602.
58. Pacelli, F., et al., *Do perioperative blood transfusions influence prognosis of gastric cancer patients? Analysis of 927 patients and interactions with splenectomy.* Ann Surg Oncol, 2011. **18**(6): p. 1615-23.
59. Yao, X.X., et al., *Radical gastrectomy with combined splenectomy: Unnecessary.* Hepato-Gastroenterology, 2011. **58**(107-108): p. 1067-1070.
60. Nashimoto, A., H. Yabusaki, and A. Matsuki, *The significance of splenectomy for advanced proximal gastric cancer.* Int J Surg Oncol, 2012. **2012**: p. 301530.
61. Wang, F., et al., *Prognostic significance of splenectomy for patients with gastric adenocarcinoma undergoing total gastrectomy: A retrospective cohort study.* International Journal of Surgery, 2014. **12**(6): p. 557-565.
62. Zhang, H., et al., *Is concomitant splenectomy beneficial for the long-term survival of patients with gastric cancer undergoing curative gastrectomy? A single-institution study.* World J Surg Oncol, 2014. **12**: p. 193.
63. Pan, D., et al., *Effect of Splenectomy Combined with Resection for Gastric Carcinoma on Patient Prognosis.* Med Sci Monit, 2016. **22**: p. 4205-4209.
64. Usui, S., et al., *Spleen preservation versus splenectomy in laparoscopic total gastrectomy with D2 lymphadenectomy for gastric cancer: A comparison of short-term outcomes.* Asian J Endosc Surg, 2016. **9**(1): p. 5-13.
65. Ji, X., et al., *Comparison of different methods of splenic hilar lymph node dissection for advanced upper- and/or middle-third gastric cancer.* BMC Cancer, 2016a. **16**(1).
66. Ji, F., et al., *Effect of splenectomy on the survival of patients underwent radical surgery for gastric cardia cancer.* International Journal of Clinical and Experimental Medicine, 2016b. **9**(11): p. 22217-22221.
67. Ohkura, Y., et al., *Efficacy of prophylactic splenectomy for proximal advanced gastric cancer invading greater curvature.* World J Surg Oncol, 2017. **15**(1): p. 106.
68. Sano, T., et al., *Randomized Controlled Trial to Evaluate Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma.* Ann Surg, 2017. **265**(2): p. 277-283.
69. Son, S.Y., et al., *Spleen-preserving lymphadenectomy versus splenectomy in laparoscopic total gastrectomy for advanced gastric cancer.* Surg Oncol, 2017. **26**(2): p. 207-211.

70. Jeong, O., et al., *Adverse prognostic impact of splenectomy on survival in gastric carcinoma patients: Regression and propensity score matching analysis of 1074 patients.* PLoS One, 2018. **13**(9): p. e0203820.
71. Ding, P., et al., *Risk evaluation of splenic hilar or splenic artery lymph node metastasis and survival analysis for patients with proximal gastric cancer after curative gastrectomy: A retrospective study.* BMC Cancer, 2019. **19**(1).
72. Ito, S., et al., *Efficacy of Splenectomy for Proximal Gastric Cancer with Greater Curvature Invasion or Type 4 Tumor: a Propensity Score Analysis of a Multi-Institutional Dataset.* World J Surg, 2021. **45**(9): p. 2840-2848.
73. Kinoshita, T., et al., *Can laparoscopic spleen-preserving splenic hilar lymph node dissection replace prophylactic splenectomy for proximal advanced gastric cancers that invade the greater curvature?* Eur J Surg Oncol, 2021. **47**(6): p. 1466-1472.
74. Davis, C.J., D.M. Ilstrup, and J.H. Pemberton, *Influence of splenectomy on survival rate of patients with colorectal cancer.* Am J Surg, 1988. **155**(1): p. 173-9.
75. Varty, P.P., I.P. Linehan, and P.B. Boulos, *Does concurrent splenectomy at colorectal cancer resection influence survival?* Dis Colon Rectum, 1993. **36**(6): p. 602-6.
76. Konstadoulakis, M.M., et al., *Long term effect of splenectomy on patients operated on for cancer of the left colon: a retrospective study.* Eur J Surg, 1999. **165**(6): p. 583-7.
77. Wakeman, C.J., et al., *The impact of splenectomy on outcome after resection for colorectal cancer: a multicenter, nested, paired cohort study.* Dis Colon Rectum, 2008. **51**(2): p. 213-7.
78. Kyriazanos, I.D., et al., *Impact of splenectomy on the early outcome after oesophagectomy for squamous cell carcinoma of the oesophagus.* Eur J Surg Oncol, 2002. **28**(2): p. 113-9.
79. Gockel, I., W. Kneist, and T. Junginger, *Influence of splenectomy on perioperative morbidity and long-term survival after esophagectomy in patients with esophageal carcinoma.* Dis Esophagus, 2005. **18**(5): p. 311-5.
80. Black, E., et al., *Unplanned splenectomy during oesophagectomy does not affect survival.* Eur J Cardiothorac Surg, 2006. **29**(2): p. 244-7.
81. Pultrum, B.B., et al., *Impact of splenectomy on surgical outcome in patients with cancer of the distal esophagus and gastro-esophageal junction.* Dis Esophagus, 2008. **21**(4): p. 334-9.
82. Aminian, A., et al., *Influence of splenectomy on morbidity of esophageal cancer surgery.* Scand J Surg, 2010. **99**(1): p. 9-13.
83. Fukuchi, M., et al., *Prognostic Impact of Splenectomy in Patients with Esophagogastric Junction Carcinoma.* In Vivo, 2018. **32**(1): p. 145-149.
84. Nagasue, N., et al., *Role of splenectomy in hepatic resection for hepatocellular carcinoma associated with severe cirrhosis and hypersplenism.* Hepatology Research, 1999. **14**(1): p. 35-48.
85. Oh, J.W., et al., *The role of splenectomy in patients with hepatocellular carcinoma and secondary hyperplenism.* Yonsei Medical Journal, 2003. **44**(6): p. 1053-1058.
86. Wu, C.C., et al., *Appraisal of concomitant splenectomy in liver resection for hepatocellular carcinoma in cirrhotic patients with hypersplenic thrombocytopenia.* Surgery, 2004. **136**(3): p. 660-8.
87. Chen, X.P., et al., *Use of hepatectomy and splenectomy to treat hepatocellular carcinoma with cirrhotic hypersplenism.* Br J Surg, 2005. **92**(3): p. 334-9.
88. Jiang, B., et al., *Surgical treatment of hepatocellular carcinoma with cirrhotic esophageal varices and hypersplenism: a 184 case report.* Front Med China, 2007. **1**(1): p. 24-9.

89. Sugimachi, K., et al., *Appraisal of hepatic resection in the treatment of hepatocellular carcinoma with severe thrombocytopenia.* World J Surg, 2008. **32**(6): p. 1077-81.
90. Kim, S.H., et al., *Role of splenectomy in patients with hepatocellular carcinoma and hypersplenism.* ANZ J Surg, 2013. **83**(11): p. 865-70.
91. Li, C., et al., *Prognosis of patients with hepatocellular carcinoma and hypersplenism after surgery: a single-center experience from the People's Republic of China.* Onco Targets Ther, 2014. **7**: p. 957-64.
92. Zhang, X.Y., et al., *Synchronous splenectomy and hepatectomy for patients with hepatocellular carcinoma and hypersplenism: A case-control study.* World J Gastroenterol, 2015. **21**(8): p. 2358-66.
93. Yang, T., et al., *Surgery for hepatocellular carcinoma presenting with variceal bleeding: The eastern experience.* J Surg Oncol, 2016. **113**(2): p. 165-74.
94. Zhang, X., et al., *Synchronous splenectomy and hepatectomy for patients with small hepatocellular carcinoma and pathological spleen: neutrophil to lymphocyte ratio changes can predict the prognosis.* Oncotarget, 2017.
95. Takeishi, K., et al., *Impact of Splenic Volume and Splenectomy on Prognosis of Hepatocellular Carcinoma Within Milan Criteria After Curative Hepatectomy.* World J Surg, 2018. **42**(4): p. 1120-1128.
96. Pei, Y., et al., *Improved survival following splenectomy combined with curative treatments for hepatocellular carcinoma in Child B patients: A propensity score matching study.* Hepatol Res, 2019. **49**(2): p. 177-188.
97. Zhou, C., et al., *Splenectomy before hepatectomy for patients with hepatocellular carcinoma and hypersplenism: A retrospective study.* Medicine (Baltimore), 2021. **100**(4): p. e24326.
98. Lewis, S.M., A. Williams, and S.C. Eisenbarth, *Structure and function of the immune system in the spleen.* Sci Immunol, 2019. **4**(33).
99. Wu, C., Q. Hua, and L. Zheng, *Generation of Myeloid Cells in Cancer: The Spleen Matters.* Front Immunol, 2020. **11**: p. 1126.
100. Hull, C.C., et al., *Splenectomy and the induction of murine colon cancer.* Arch Surg, 1988. **123**(4): p. 462-4.
101. Li, L., et al., *The spleen in liver cirrhosis: revisiting an old enemy with novel targets.* J Transl Med, 2017. **15**(1): p. 111.
102. Li, Z.F., et al., *Changes in count and function of splenic lymphocytes from patients with portal hypertension.* World J Gastroenterol, 2008. **14**(15): p. 2377-82.
103. Li, A., et al., *Dysfunction of splenic macrophages in cirrhotic patients with hypersplenism and HBV infection.* Am J Med Sci, 2008. **336**(1): p. 32-8.
104. Ren, S., et al., *NF-kappaB p65 and c-Rel subunits promote phagocytosis and cytokine secretion by splenic macrophages in cirrhotic patients with hypersplenism.* Int J Biochem Cell Biol, 2013. **45**(2): p. 335-43.
105. Li, J., et al., *Splenic serum from portal hypertensive patients enhances liver stem cell proliferation and self-renewal via the IGF-II/ERK signaling pathway.* Dig Liver Dis, 2020. **52**(2): p. 205-213.
106. Velazquez, R.F., et al., *Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis.* Hepatology, 2003. **37**(3): p. 520-7.
107. Li, L., et al., *The Spleen Promotes the Secretion of CCL2 and Supports an M1 Dominant Phenotype in Hepatic Macrophages During Liver Fibrosis.* Cell Physiol Biochem, 2018. **51**(2): p. 557-574.
108. Zheng, Z., et al., *Splenectomy enhances the Ly6C(low) phenotype in hepatic macrophages by activating the ERK1/2 pathway during liver fibrosis.* Int Immunopharmacol, 2020. **86**: p. 106762.

109. Huang, N., et al., *Spleen-Associated Effects on Immunity in Hepatitis B Virus-Related Cirrhosis with Portal Hypertension.* J Interferon Cytokine Res, 2019. **39**(2): p. 95-105.
110. Huang, N., et al., *Effect of Splenectomy on Serum Cytokine Profiles in Hepatitis B Virus-Related Cirrhosis Patients with Portal Hypertension.* Viral Immunol, 2018. **31**(5): p. 371-378.
111. Ji, F., et al., *Splenectomy prior to antiviral therapy in patients with hepatitis C virus related decompensated cirrhosis.* Braz J Infect Dis, 2013. **17**(5): p. 601-5.
112. Nomura, Y., et al., *Influence of splenectomy in patients with liver cirrhosis and hypersplenism.* Hepatol Res, 2014. **44**(10): p. E100-9.
113. Sugawara, Y., et al., *Splenectomy in patients with hepatocellular carcinoma and hypersplenism.* J Am Coll Surg, 2000. **190**(4): p. 446-50.
114. Li, B., et al., *Dynamics of the spleen and its significance in a murine H22 orthotopic hepatoma model.* Exp Biol Med (Maywood), 2016. **241**(8): p. 863-72.
115. Li, B.H., et al., *The spleen contributes to the increase in PMN-MDSCs in orthotopic H22 hepatoma mice.* Mol Immunol, 2020. **125**: p. 95-103.
116. Higashijima, J., et al., *Effect of splenectomy on antitumor immune system in mice.* Anticancer Research, 2009. **29**(1): p. 385-393.
117. Imai, S., et al., *Effects of splenectomy on pulmonary metastasis and growth of SC42 carcinoma transplanted into mouse liver.* J Surg Oncol, 1991. **47**(3): p. 178-87.
118. Miller, M.R., et al., *Splenectomy promotes indirect elimination of intraocular tumors by CD8+ T cells that is associated with IFNγ- and Fas/FasL-dependent activation of intratumoral macrophages.* Cancer immunology research, 2014. **2**(12): p. 1175-1185.
119. Wang, Q., et al., *Is concomitant splenectomy necessary in radical gastric cancer surgery? A systematic review and meta-analysis.* Asia Pac J Clin Oncol, 2019. **15**(2): p. e28-e35.
120. Liu, X., et al., *Safety of Simultaneous Hepatectomy and Splenectomy in the Treatment of Hepatocellular Carcinoma Complicated with Hypersplenism: A Meta-analysis.* Gastroenterol Res Pract, 2019. **2019**: p. 9065845.
121. Li, W., et al., *Simultaneous hepatectomy and splenectomy versus hepatectomy alone for hepatocellular carcinoma complicated by hypersplenism: a meta-analysis.* Onco Targets Ther, 2015. **8**: p. 2129-37.
122. Yang, K., et al., *Effectiveness and safety of splenectomy for gastric carcinoma: a meta-analysis.* World J Gastroenterol, 2009. **15**(42): p. 5352-9.
123. Marano, L., et al., *Oncologic Effectiveness and Safety of Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma: Meta-analysis of Randomized Controlled Trials.* Anticancer Res, 2018. **38**(6): p. 3609-3617.
124. Kunisaki, C., et al., *Systemic Review and Meta-analysis of Impact of Splenectomy for Advanced Gastric Cancer.* In Vivo, 2020. **34**(6): p. 3115-3125.

Tables

Table 1. Meta-analyses of cancer risk after splenectomy

Outcome	Studies, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)	P Value for Egger´s test
All cancers	8	1.476 (1.182, 1.843)	0.001	67.3 (<0.001)	89.6%	0.779
Liver cancer	7	1.436 (0.469, 4.397)	0.469	255.7 (<0.001)	97.7%	0.918
Lung cancer	7	1.28 (1.145, 1.440)	<0.001	7.06 (0.315)	15.0%	0.690
NHL	7	3.867 (2.055, 7.277)	<0.001	20.99 (0.002)	71.4%	0.891
Leukemia	6	5.376 (4.431, 6.523)	<0.001	7.59 (0.180)	34.1%	0.915
Colorectal cancer	6	1.152 (0.919,1.444)	0.219	5.88 (0.319)	14.9%	0.316
Breast cancer	6	1.574 (1.105, 2.242)	0.012	4.93 (0.425)	0%	0.126
Oral and pharyngeal cancer	6	1.285 (1.034, 1.598)	0.024	3.18 (0.673)	0%	0.689
Skin cancer	5	1.760 (1.004, 3.088)	0.049	1.52 (0.823)	0%	NA
Esophagus cancer	5	2.058 (1.529, 2.770)	<0.001	6.86 (0.144)	41.7%	NA
Prostate cancer	5	1.253 (1.070, 1.467)	0.005	4.26 (0.372)	6.0%	NA
Bladder cancer	5	1.300 (1.005, 1.683)	0.046	2.64 (0.618)	0%	NA
Gastric cancer	4	1.920 (1.394, 2.643)	<0.001	4.30 (0.231)	30.2%	NA
Pancreas cancer	3	1.779 (1.228, 2.577)	0.002	0.80 (0.670)	0%	NA
Kidney cancer	2	1.121 (0.724, 1.736)	0.610	1.18 (0.278)	15.2%	NA
HL	2	6.714 (1.502, 30.003)	0.013	2.93 (0.087)	65.9%	NA
Brain and nervous system cancer	2	3.941 (1.080, 14.380)	0.038	0.44 (0.509)	0%	NA

CI = confidence intervals, NHL = Non Hodgkin Lymphoma, HL = Hodgkin Lymphoma.

Table 2. Subgroup meta-analyses of cancer risk based on reason of splenectomy

Outcome	Studies, n	Reason of splenectomy	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)
All cancers	4	Trauma	1.304 (1.088, 1.562)	0.004	7.93 (0.048)	62.0%
All cancers	4	Notrauma	1.741 (1.146, 2.644)	0.009	31.17 (<0.001)	90.4%
Liver cancer	2	Protal hypertension	0.524 (0.423, 0.649)	<0.001	0.001 (0.965)	0%
Liver cancer	3	Trauma	2.068 (1.525, 2.805)	<0.001	0.44 (0.804)	0%
Lung cancer	4	Trauma	1.244 (1.102, 1.405)	<0.001	0.42 (0.936)	0%
Lung cancer	3	Notrauma	1.675 (1.176, 2.386)	0.004	4.22 (0.121)	52.6%
NHL	4	Trauma	3.086 (2.400, 3.968)	<0.001	2.06 (0.560)	0%
NHL	3	Notrauma	6.111 (1.979, 18.870)	0.002	10.04 (0.007)	80.1%
Leukemia	3	Trauma	5.178 (4.226, 6.345)	<0.001	0.32 (0.853)	0%
Leukemia	3	Notrauma	7.693 (4.103, 14.423)	<0.001	5.89 (0.053)	66.1%
Colorectal cancer	3	Trauma	1.203 (0.926, 1.564)	0.167	5.15 (0.076)	61.1%
Colorectal cancer	3	Notrauma	1.017 (0.653, 1.585)	0.939	0.32 (0.851)	0%
Breast cancer	3	Trauma	1.473 (0.829, 2.616)	0.186	4.10 (0.129)	51.2%
Breast cancer	3	Notrauma	1.639 (1.046, 2.568)	0.031	0.74 (0.690)	0%
Oral and pharyngeal cancer	4	Trauma	1.265 (1.011, 1.583)	0. 04	2.05 (0.5561)	0%

Oral and pharyngeal cancer	2	Notrauma	1.666 (0.674, 4.118)	0.269	0.79 (0.357)	0%
Skin cancer	2	Trauma	1.267 (0.365, 4.394)	0.709	0.63 (0.427)	0%
Skin cancer	3	Notrauma	1.915 (1.020, 3.596)	0.043	0.55 (0.759)	0%
Esophagus cancer	3	Trauma	1.855 (1.345, 2.559)	<0.001	3.95 (0.139)	49.4%
Esophagus cancer	2	Notrauma	3.773 (1.735, 8.023)	0.001	0.17 (0.683)	0%
Prostate cancer	3	Trauma	1.236 (1.052, 1.460)	0.010	1.65 (0.437)	0%
Prostate cancer	2	Notrauma	1.445 (0.802, 2.604)	0.220	2.36 (0.124)	57.6%
Bladder cancer	3	Trauma	1.237 (0.929, 1.647)	0.146	1.58 (0.454)	0%
Bladder cancer	2	Notrauma	1.651 (0.891, 2.928)	0.115	0.44 (0.508)	0%
Gastric cancer	2	Trauma	1.690 (1.133, 2.523)	0.010	1.37(0.242)	27.1%
Gastric cancer	2	Notrauma	2.402 (1.412, 4.087)	0.001	1.85 (0.173)	46.1%
Pancreas cancer	2	Trauma	1.864 (1.268, 2.740)	0.002	0.05 (0.822)	0%

CI = confidence intervals, NHL = Non Hodgkin Lymphoma.

Table 3. Meta-analyses of 5-year OS after splenectomy

Outcome	Studies, n	SP+, n	SP-, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)	P Value for Egger´s test
Gastric cancer	39	5079	8098	0.787 (0.734, 0.844)	<0.001	95.18 (<0.001)	60.1%	0.163
Liver cancer	10	645	901	1.173 (1.076, 1.279)	<0.001	14.92 (0.093)	39.7%	0.237
Colorectal cancer	4	158	158	0.769 (0.555, 0.859)	0.001	0.30 (0.963)	0%	NA
esophageal cancer and esophago-gastric junction cancer	3	120	554	0.541 (0.397, 0.737)	<0.001	3.07 (0.216)	34.8%	NA

CI = confidence intervals, OS = overall survival, NA = data not available.

Table 4. Subgroup meta-analyses of 5-year OS after splenectomy for gastric cancer

Subgroup	Studies, n	SP+, n	SP-, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)
RCT	4	572	596	0.988 (0.882, 1.108)	0.841	3.92 (0.270)	23.5%
nRCT	35	4507	7502	0.760 (0.712, 0.810)	<0.001	59.87 (0.004)	43.2%
Total gastrectomy	23	2763	2483	0.818 (0.747, 0.895)	<0.001	57.29 (<0.001)	61.6%
Pancreasectomy	5	222	1134	0.565(0.434, 0.735)	<0.001	7.16 (0.127)	44.2%
Nopancreasectomy	17	2103	2644	0.845 (0.765, 0.933)	0.001	45.54 (<0.001)	64.9%
Stage□	5	230	819	0.936 (0.839, 1.044)	0.235	1.99 (0.738)	0%
Stage □	7	259	802	0.821 (0.707, 0.953)	0.010	4.00 (0.177)	0%
Stage □	8	743	1144	0.723 (0.618, 0.846)	<0.001	2.02 (0.959)	0%
Stage □	4	236	422	1.048 (0.545, 2.014)	0.889	4.25 (0.236)	29.4%

CI = confidence intervals, OS = overall survival, NA = data not available.

Table 5. Meta-analyses of mortality after splenectomy

Outcome	Studies, n	SP+, n	SP-, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)	P Value for Egger´s test
Gastric cancer	26	4544	8947	1.461 (1.229, 1.736)	<0.001	47.31 (0.005)	47.2%	0.371
Liver cancer	9	406	1135	1.572 (0.757, 3.080)	0.237	1.77 (0.987)	0%	0.319
esophageal cancer and esophago-gastric junction cancer	5	176	1745	1.658 (0.948, 2.900)	0.076	7.65 (0.105)	47.7%	NA

CI = confidence intervals, NA = data not available.

Table 6. Meta-analyses of complications after splenectomy for gastric cancer

Outcome	Studies, n	SP+, n	SP-, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)	P Value for Egger´s test
Total complications	35	4115	8040	1.818 (1.523, 2.171)	<0.001	175.94 (<0.001)	80.7%	0.048
Anastomotic leakage	24	2789	4895	1.853 (1.501, 2.288)	<0.001	19.42 (0.677)	0%	0.248
Pulmonary complication	22	2554	3075	1.584 (1.257, 1.996)	<0.001	12.30 (0.931)	0%	0.219
Ileus	16	2268	3972	1.169 (0.875, 3.523)	0.289	15.76 (0.398)	4.8%	0.374
Postoperative bleeding	16	2066	2563	1.302 (0.823, 2.060)	0.259	14.75 (0.470)	0%	0.383
Intraabdominal abscess	15	1952	4081	2.914 (1.672, 5.081)	<0.001	42.67 (<0.001)	67.2%	0.612
Pancreatic fistula	14	1728	3426	5.390 (2.571, 11.298)	<0.001	48.77 (<0.001)	73.3%	0.838
Wound infection	10	1234	1466	1.461 (1.023, 2.088)	0.037	5.84 (0.756)	0%	0.362
Cardiac complication	8	1193	1393	0.850 (0.417, 1.733)	0.654	4.95 (0.665)	0%	0.250
Liver dysfunction	6	915	737	1.213 (0.681, 2.163)	0.512	2.66 (0.753)	0%	0.024
Pancreatits	5	614	2236	1.391 (0.812, 2.384)	0.229	5.57 (0.234)	28.2%	NA
Anastomotic stenosis	5	474	673	1.029 (0.374, 2.834)	0.955	3.43 (0.489)	0%	NA
Renal dysfunction	4	562	479	3.135 (0.862, 11.399)	0.083	1.30 (0.729)	0%	NA
Sepsis	3	508	642	1.457 (0.165, 12.859)	0.735	6.81 (0.033)	70.6%	NA

CI = confidence intervals.

Table 7. Meta-analyses of complications after splenectomy for liver cancer

Outcome	Studies, n	SP+, n	SP-, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)	P Value for Egger´s test
Total complications	10	561	1087	1.124 (0.949, 1.331)	0.176	10.67 (0.299)	15.7%	0.073
Postoperative bleeding	10	683	1425	2.230 (1.077, 4.617)	0.031	2.44 (0.982)	0%	0.971
Pleural effusion	8	478	1059	1.433 (0.953, 2.155)	0.084	2.41 (0.934)	0%	0.919
Bile leakage	6	425	938	1.156 (0.497, 2.688)	0.736	2.99 (0.705)	0%	0.288
Ascites	6	281	827	1.340 (0.829, 2.165)	0.232	3.54 (0.618)	0%	0.383
Wound infection	6	425	536	1.291 (0.542, 3.072)	0.564	3.34 (0.648)	0%	0.381
Upper gastrointestinal haemorrhage	5	351	893	1.143 (0.447, 2.922)	0.780	3.44 (0.487)	0%	NA
Pulmonary infection	5	287	842	1.954 (0.693, 5.511)	0.205	1.33 (0.857)	0%	NA
Liver failure	4	251	348	1.003 (0.337, 2.986)	0.995	0.68 (0.878)	0%	NA
PSVT	3	174	255	23.912 (6.782, 80.306)	<0.001	2.55 (0.279)	21.6%	NA

CI = confidence intervals, PSVT = portal vein or splenic vein thrombosis.

Table 8. Meta-analyses of complications after splenectomy for esophageal and esophago-gastric junction cancer

Outcome	Studies, n	SP+, n	SP-, n	Risk Ratio (95% CI)	P Value	Heterogeneity χ2(P value)	Inconsistency I^2(%)
Leakage	5	176	1745	1.935 (1.116, 3.355)	0.019	14.43 (0.006)	72.3%
Pulmonary complications	5	176	1745	1.229(0.679, 2.225)	0.495	25.62 (<0.001)	84.4%
Cardiac complications	5	176	1745	0.972 (0.622, 1.518)	0.899	1.77 (0.778)	0%
Wound infection	3	128	969	0.980 (0.495, 1.9437)	0.955	1.25 (0.535)	0%
Postoperative bleeding	3	114	649	0.733 (0.010, 4.943)	0.750	4.10 (0.128)	51.3%

CI = confidence intervals.

Supplementary Files

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