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Autologous platelet scintigraphy and clinical outcome of splenectomy in immune thrombocytopenia: A systematic review and meta-analysis

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ABSTRACT

Autologous platelet sequestration pattern is associated with post-splenectomy platelet response in patients with immune thrombocytopenia (ITP). However, published results are contradictory, and have not been systematically reviewed. Our aim is to systematically review and meta-analyse the association between sequestration pattern and post-splenectomy platelet response. Articles were selected from MEDLINE when they a) included ITP patients, b) performed scintigraphy, and c) included post-splenectomy platelet response. The 23 included studies (published between 1969–2018) represented 2966 ITP-patients. Response to splenectomy occurred most frequently in patients with a splenic pattern (87.1 % in splenic versus 47.1 % in mixed and 25.5 % in hepatic patterns). A pooled analysis of 8 studies showed an odds ratio of 14.21 (95 % CI: 3.65–55.37) for platelet response in the splenic versus the hepatic group. Our findings indicate that a splenic sequestration pattern is associated with better response after splenectomy. Platelet sequestration patterns may be useful in the clinical decision-making regarding splenectomy.

1. Introduction

Immune thrombocytopenia (ITP) is a hematological auto-immune disorder characterized by low platelet counts and risk of bleeding. The mechanisms that lead to low platelet counts in ITP are complex, multifactorial, and not completely understood. Mechanisms that have been described include the increased clearance of auto-antibody-opsonized platelets in liver and spleen. (Chaturvedi et al., 2018; Abadi et al., 2015; Kashiwagi and Tomiyama, 2013) The main sites of platelet destruction are the liver and the spleen. In addition, the spleen is also a major source of anti-platelet autoantibodies (Aslam et al., 2016; Misiakos et al., 2017; Sandler, 2000).

The treatment for ITP consists of therapies that a) reduce the auto-antibody production, b) stimulate the platelet production, or c) inhibit platelet clearance by either intravenous immunoglobulin (IVIG) treatment or performing a splenectomy. (Bylsma et al., 2019; Grace and Neunert, 2016; Lambert and Gernsheimer, 2017) Splenectomy can induce long-term (5-year) remission rates in approximately 60–70 % of ITP patients. (Tastaldi et al., 2019; Rijcken et al., 2014; Ahmed et al., 2016; Vianelli et al., 2005) The complication and mortality rate of laparoscopic and laparotomic splenectomy is 0.2 % and 7–10 % respectively. (Tastaldi et al., 2019; Rijcken et al., 2014; Kojouri et al., 2004) Additionally, post-splenectomy patients have a life-long susceptibility of thrombosis and infections with encapsulated bacteria, despite vaccine prophylaxis. (Leone and Pizzigallo, 2015) Given these complications and the non-response rate of 30–40 % of the patients after splenectomy, it is important to investigate predictors of post-splenectomy platelet response.

Possible predictors that were studied for post-splenectomy platelet response include: age, duration of disease, responses to first-line therapies, platelet-bound immunoglobulin, platelet turnover and lifespan, and the site of platelet destruction. (Sarpatwari et al., 2010) None of these predictors are widely implemented in clinical practice, partly due to heterogenous study results. (Kojouri et al., 2004; Sarpatwari et al., 2010; Navez et al., 2015).

Platelet scintigraphy can directly visualize and monitor the site of platelet sequestration and the dynamics of platelets through 51-chromium (51-Cr) or 111-indium (111-In) labelled autologous platelets. The

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sequestration patterns from scintigraphy seem to be associated with post-splenectomy platelet response.

(Taylor et al., 2006; Palandri et al., 2014; Najean et al., 1997). However, studies show heterogenous results and the clinical usefulness of sequestration patterns in the decision-making regarding splenectomy is still debated. (Kojouri et al., 2004; Sarpatwari et al., 2010; Richards and Thompson, 1979) Apart from a mini-review published in 2010, no systematic review or meta-analysis has been performed. (Cuker and Cines, 2010) This study aims to systematically review and meta-analyse the association between sequestration patterns and platelet response after splenectomy in ITP patients.

2. Methods

2.1. Literature search

The following databases were searched: PubMed, Embase (OVID-version), Web of Science, Cochrane Library, Emcare, Academic Search Premier, and ScienceDirect. The search query consisted of the combination of the following keywords: 'Diagnostic imaging of the Spleen' and 'Immune thrombocytopenia'. The complete search syntax can is described in Supplementary Table 1. Results were limited to articles published in English, Dutch, German, French, or Italian. There were no restrictions for the publication date of the studies and the final search was performed on December 6th, 2018. Each article was reviewed independently by two researchers for inclusion according to prior established inclusion- and exclusion criteria. Any disagreements were resolved by discussion with a third party. The article selection procedure can be found in the study flow diagram, shown in Fig. 1. This study was carried out in accordance with PRISMA guidelines. This review has been registered in PROSPERO under registration number CRD42018104632.

2.2. Inclusion-and exclusion criteria

Articles were included when they a) included ITP patients, b) performed scintigraphy to determine the sequestration site of platelets and c) included post-splenectomy platelet outcomes. Studies which focused on scintigraphy technique and did not mention clinical outcomes were excluded from this review. Studies with a population of ≤5 patients were excluded.

2.3. Data extraction

Data from included articles were extracted independently by two researchers using a standardized form. These data included patients' sex and age, ITP duration, previous ITP treatments platelet count at time of scan, interval measurements part of the scintigraphy procedure, use of nuclear agent, sequestration pattern, definition of sequestration pattern, splenectomy, definition of platelet response, platelet response post-splenectomy (Complete Response (CR), Partial Response (PR), Non Response (NR) and/or absolute mean or median platelet count if given), platelet survival time, follow up time and complications of splenectomy.

2.4. Definition of sequestration pattern and post-splenectomy platelet response

Sequestration patterns will be grouped in a) splenic, b) hepatic, and c) mixed. Post-splenectomy platelet response will be grouped in a) Complete Response (CR), b) Partial Response (PR), and c) Non-Response (NR)using the definitions from the ASH 2011 Guideline. (Neunert et al., 2011) Differences in the definitions of a sequestration pattern and response rates will be summarized in **Supplementary table 2**.

2.5. Data synthesis and pooled analysis

Baseline data of study characteristics will be shown using descriptive statistics. The main analysis focusses on the association between sequestration pattern and post-splenectomy platelet response. First, the absolute response rates after splenectomy between the different sequestration groups will be compared. Second, a pooled analysis will compare splenectomy outcome in patients with a splenic sequestration pattern versus hepatic sequestration pattern. Pooled Odds Ratios (OR) and a Forest plot will be used to summarize this pooled analysis,

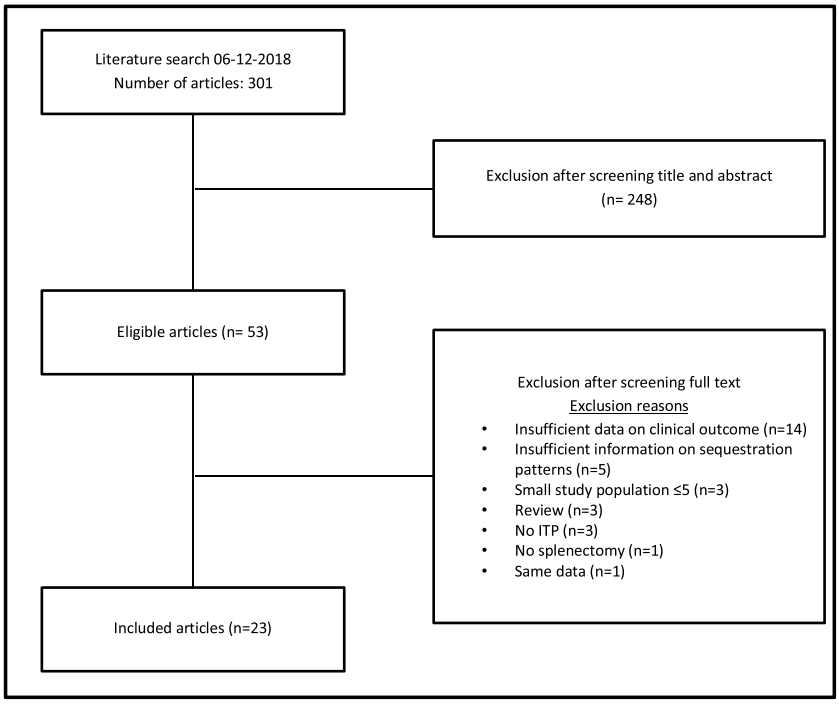


Fig. 1. Search strategy.

using RevMan 5. Additional analyses will consist of comparing splenic versus non-splenic sequestration groups and hepatic versus non-hepatic sequestration groups. Furthermore, similar analyses will be performed in studies with a median follow-up time of 24 months or longer to compare the long-term versus the short-term response rates of splenectomy.

2.6. Risk of Bias assessment

Study quality was assessed by two independent researchers using two tools: a) the Newcastle Ottawa Scale (NOS) for cohort studies (GA Wells et al., 2019) and b) the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group from the National Heart, Lung and Blood Institute (NHLBI) (Quality Assessment, 2018). We considered studies with a lost-to-follow-up percentage of more than 20 % or studies that did not provide a description of missing items, likely to cause bias.

3. Results

3.1. Search and inclusion

The bibliographic databases yielded 301 regular references, as shown in Fig. 1. During the initial phase of exclusion, 248 articles were excluded after reading the title and abstract. Subsequently, 30 of the remaining articles were excluded after reading the full text due to a) insufficient data on clinical outcome (n = 14), b) insufficient data on sequestration patterns (n = 5), c) small study population (n = 3) and other reasons (n = 8), as shown in Fig. 1. In total, 23 articles published between 1969 and 2018 were included.

3.2. Characteristics of included studies

The 23 included studies represented a total of 2966 ITP patients, as shown in Table 1. The age of the patients ranged from 2 to 86 years, with a mean age of 40.9 years. All studies included adult patients and 15 of the 23 studies included patients under the age of 18. Across the studies, 61 % of the patients was female. The mean platelet count of the study participants at baseline was 35 × 10^9/L (n = 18 reporting studies) and the mean duration of ITP was 15.8 months at the moment of study inclusion (n = 7 reporting studies). 17 studies reported data on (previous) use of corticosteroids by their study participants and 6 of those studies described a complete or partial response to corticosteroids in some of their study participants. Other (previous) ITP treatments, like IVIG, vincristine, danazol and cyclophosphamide, were reported in 4 of the 23 studies.

The mean postoperative platelet count was 324 × 10^9/L, as reported in 11 studies. The sequestration pattern was Splenic in 54.3 %, Hepatic in 11.2 % and Mixed in 18.4 % of the patients. A splenectomy was performed in 53 % of the included patients. The proportion of splenectomy was highest in patients with Splenic sequestration (57.1 %) in comparison with Mixed (36.5 %) and Hepatic (26.7 %).

Complications of splenectomy were reported in 11 studies, with fatal complications being reported in 9 studies and 2 studies reporting no complications at all during follow-up. There was an overall mortality of 2% in the 613 splenectomised patients. The 12 remaining studies did not provide data on complications or mortality.

3.3. Risk of bias assessment

As shown in Table 1, risk of bias is scored in the Newcastle Ottawa Scale (NOS) for cohort studies and the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group from the National Heart, Lung and Blood Institute (NHLBI) for all the included studies. In the NOS tool, the mean score was 5,8 out of 8 stars (range 3–7). The NHLBI scored a mean of 6,1 of 12 (range 3–9).

3.4. Definition of sequestration pattern and post-splenectomy platelet response

All studies grouped their patients' outcome based on their sequestration pattern. However, the definition used for this grouping variable

Table 1
Characteristics of included studies.

First author	Year	Country	ITP patients (n)	M (%)	Age (mean)	Platelet count (x10^9/L)	Isotope	Splenic %	Mixed%	Hepatic%	Splenectomy (n)	Newcastle Ottawa (stars)	NHLBI (n yes)
Aster	1969	USA	15	40	55.2	31	Chromium	67	0	27	7 (47 %)	5	4
Ries	1974	USA	15	53	40.7	27.3	Chromium	93	1	0	15 (100 %)	5	4
Richards	1979	UK	22	45.5	31.4	19	Chromium	–	–	–	13 (59 %)	6	4
Gugliotta	1981	Italy	197	34	–	32	Chromium	57	37	0	111 (56 %)	5	8
Heyns	1982	South Africa	8	37.5	24.6	15.5	Indium	38	38	25	2 (25 %)	4	4
Boughton	1985	UK	14	42.9	30.9	33	Indium	50	14	36	14 (100 %)	4	3
Cola	1986	Italy	107	37.3	–	–	–	73	24	0	107 (100 %)	4	4
Gietz	1988	Germany	77	34	41	36.6	Chromium	82	0	1	51 (66 %)	5	6
Fenaux	1989	France	181	37	34	–	Chromium & Indium	–	–	–	181 (100 %)	5	8
Gernsheimer	1989	USA & Canada	19	36.8	44	57.9	Indium	–	–	–	10 (53 %)	6	8
Siegel	1989	USA	59	32.2	45.3	36	Indium	76	14	10	21 (36 %)	6	5
Najean	1971	France	575	–	–	–	Chromium	59	27	13	206 (36 %)	5	5
Najean	1991	France	222	35	–	46	Indium	57	20	23	103 (46 %)	7	7
Lamy	1993	France	105	40.5	–	25	Indium	81	11	8	51 (49 %)	6	7
Najean	1997	France	578	37.5	–	–	Indium	64	20	16	268 (46 %)	3	4
Louwes	1999	Netherlands	141	35.5	50	37	Indium	–	–	–	47 (33 %)	5	7
Uchida	2000	Japan	38	30	44	3.3	Indium	–	–	–	24 (63 %)	4	6
Rossi	2002	Italy	93	33.3	49*	24.5	Indium	–	–	–	25 (27 %)	6	9
Sarpatwari	2010	UK	256	37	38*	50	Indium	56	23	20	91 (36 %)	7	8
Roca	2011	Spain	41	63.4	45.5	31.8	Indium	–	–	–	41 (100 %)	5	9
Palandri	2014	Italy	70	34	30*	30	Indium	74	11	14	70 (100 %)	6	7
Navez	2015	Belgium	82	32	45.5	93	Indium	61	17	11	82 (100 %)	5	8
Kazi	2018	UK	51	51	43.1*	–	Indium	63	24	8	20 (39 %)	5	6
Total	**23**		**2966**	**39.1**	**40.9**	**34.9**	**6 Chrom. 15 Indium**	**65.7 (± 13.7)**	**17.6 (± 11.6)**	**13.2 (± 10.8)**	**1560** (53 %)	**5,2/8**	**6,1/12**

* Only median age is available.

Table 2a
Short-term post-splenectomy platelet response stratified by sequestration pattern.

	CR	PR	NR	Missing
Splenic (n = 822)	716 (87.1 %)	61 (7.4 %)	45 (5.5 %)	
Hepatic (n = 90)	23 (25.5 %)	16 (17.8 %)	51 (56.7 %)	
Mixed (n = 138)	65 (47.1 %)	30 (21.7 %)	43 (31.2 %)	
Unknown (n = 510)	355 (69.6 %)	22 (4.3 %)	75 (14.7 %)	58 (11.4 %)
Total (n = 1560)	1159 (74.3 %)	129 (8.3 %)	214 (13.7 %)	58 (3.7 %)

Data based on all 23 studies.CR = complete response, PR = partial response, NR = non-response.

varied substantially across the studies, was not clear or was not reported at all. Only 11 out of 23 studies provided some information on the definition of the groups, with heterogenous definitions for CR, PR and/or NR. A detailed overview of the sequestration as well as outcome definitions used in all included studies is provided in **Supplementary table 2**.

3.5. Absolute rates of splenectomy outcomes between sequestration patterns

Overall, 1560 ITP patients underwent a splenectomy of whom 63 % had a Splenic pattern, 13 % a Mixed, 6% a Hepatic pattern and 18 % Unknown pattern (missing). Absolute rates of post-splenectomy platelet response are described in Table 2a (short term; < 6 months) and Table 2b (long term; > 24 months).

For the short-term outcomes, 1159 (74.3 %) patients achieved a Complete Response, 129 (8.3 %) a Partial and 214 (13.7 %) a Non-Response. An overall post-splenectomy response (CR or PR) was seen most frequently in patients with Splenic sequestration pattern (87.1 % versus 47.1 % of the patients with Mixed sequestration and 25.5 % of the patients with Hepatic sequestration). Furthermore, more than half (56.7 %) of the patients with Hepatic sequestration did not respond to splenectomy, while only 5.5 % of the patients with splenic and 31.2 % with mixed sequestration showed a Non-Response.

A long term response of > 24 months (CR or PR) was described in 7 studies and showed a response in 317 of 379 patients (83.6 %). In 4 studies the outcomes were stratified by sequestration pattern. A long-term response (CR or PR) to splenectomy was again most frequently seen in patients with Splenic sequestration (88.8 %) versus patients with a non-Splenic sequestration (51.0 %). The response rate (PR or NR) could not be determined in 5.6 % (10/180) of the patients with a Splenic and in 29.4 % (15/51) of the patients with a non-Splenic sequestration.

3.6. Meta-analysis on association between sequestration pattern and post-splenectomy response

Eight studies provided data on post-splenectomy response rates that were stratified by sequestration pattern. These studies were eligible for pooled analysis. The Odds Ratio (OR) for a treatment response for the Splenic sequestration pattern was 14.21 [95 % CI 3.65,55.37] compared to the Hepatic sequestration pattern, with a substantial heterogeneity between the studies (I^2 of 74 %), as shown in Table 3**a**. An additional sensitivity analysis using four studies with well-defined criteria/definitions for both the sequestration patterns and post-splenectomy response resulted in a comparable OR of 9.21 [1.70,49.99] and I^2 of 67 %, as shown in Table 3**b**. Additional analyses comparing Splenic versus non-Splenic and Non-Hepatic versus Hepatic showed an OR of 7.36 [2.58, 21.03] and 8.96 [3.12, 25.70] respectively, as shown in **Supplementary table 2a and 2b**.

Table 2b
Long-term post-splenectomy platelet response stratified by sequestration pattern.

	n	CR + PR	NR or relapse	Unknown (PR, NR or relapse)
Splenic	180	160 (888%)	10 (5,6%)	10 (5,6%)
Non-splenic	51	26 (510%)	10 (196%)	15 (294%)

Data based on 4 studies: Sarpatwari (Sarpatwari et al., 2010), Navez (Navez et al., 2015), Kazi (Kazi et al., 2019), Palandri (Palandri et al., 2014) CR = complete response, PR = partial response, NR = non-response.

4. Discussion

Our main objective was to systematically review and meta-analyse the evidence available on the association between sequestration pattern and post-splenectomy platelet response in ITP patients. Patients with a Splenic sequestration pattern showed the highest post-splenectomy response rate (87.1 %) versus the Mixed (47.1 %) and Hepatic patterns (25.5 %). Furthermore, over half of the patients with a Hepatic sequestration patterns showed no platelet response after splenectomy, while only 5.5 % of the patients with a Splenic pattern showed a non-response post-splenectomy. A pooled analysis based on 8 studies showed an OR for post-splenectomy platelet response of 14.21 [3.65–55.37] in favour of the Splenic sequestration group versus the Hepatic group.

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the association between sequestration pattern and post-splenectomy platelet response in ITP patients. Analyses on short-term post-splenectomy platelet response are similar to results described in the mini review by Cuker and Cines from 2010. The present study included an additional 17 studies compared to this mini-review, most likely due to a more comprehensive literature search (301 versus 51 hits) and the inclusion of 4 studies published after 2010.

While most studies on this association focussed on short term outcomes (follow-up of less than 2 years), this meta-analysis included 8 studies with a longer follow-up time (up to 5 years). Analyses on the long-term post-splenectomy platelet response showed similar results compared to the short-term outcomes, in which 88.8 % of the patients with a Splenic pattern showed a post-splenectomy platelet response compared to 51.0 % in the Hepatic group.

Factors that may influence the association between sequestration pattern and post-splenectomy platelet response are unknown. We could however extract some factors from our data that might be of interest regarding the association: a) Younger patients showed a predominantly Splenic sequestration pattern, where Hepatic or Mixed patterns are more frequently seen in older patients (Gugliotta, 1981, Najean et al., 1997, Najean, 1991, Najean, 1971), b) There was a trend where patients with Hepatic sequestration had a longer duration of disease from clinical onset (Najean, 1971), c) Primary ITP showed a more Splenic pattern, while secondary ITP showed a more Hepatic pattern (Rossi, 2002). No clear differences were observed in platelet counts between Splenic and non-Splenic patients (Najean, 1991, Najean et al., 1997). These factors could play a role as a confounder on the association between sequestration pattern and post-splenectomy platelet response. Future studies should provide a baseline table stratified by sequestration pattern and perform multivariable analysis, including possible confounders.

4.1. Limitations

The results of this study need to be interpreted with the following limitations in mind.

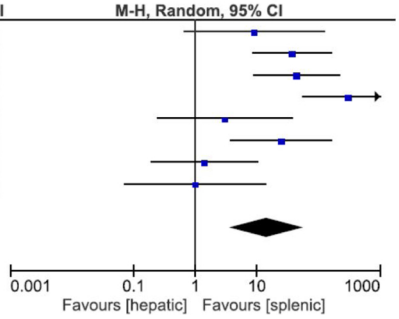
First, due to the observational nature of the included studies, we cannot draw definitive causal conclusions. However, a randomized controlled trial might not be feasible for this research question. When investigating the association between sequestration pattern and post-splenectomy platelet response, it is important to take confounders into account. None of the included studies provided a stratified baseline

Table 3
Pooled analysis and Forest Plot on the association between sequestration pattern and post-splenectomy platelet response.

a. Including all 8 studies

Study or Subgroup	Splenic sequestration Events	Total	Hepatic sequestration Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Cola 1986	73	77	2	3	10.6%	9.13 [0.68, 123.22]
Najean 1971	155	166	3	11	14.5%	37.58 [8.72, 161.97]
Najean 1991	73	76	5	14	14.0%	43.80 [8.93, 214.79]
Najean 1997	209	212	3	16	13.7%	301.89 [55.40, 1645.17]
Navez 2015	48	50	8	9	10.9%	3.00 [0.24, 37.08]
Palandri 2014	50	52	5	10	13.0%	25.00 [3.82, 163.83]
Rossi 2002	14	18	5	7	12.7%	1.40 [0.19, 10.15]
Siegel 1989	10	15	2	3	10.5%	1.00 [0.07, 13.87]
Total (95% CI)		**666**		**73**	**100.0%**	**14.21 [3.65, 55.37]**
Total events	632		33			

Heterogeneity: Tau² = 2.77; Chi² = 26.97, df = 7 (P = 0.0003); I² = 74%
Test for overall effect: Z = 3.83 (P = 0.0001)



b. Including 4 studies with well-defined definitions

Study or Subgroup	Splenic pattern Events	Total	Non-splenic pattern Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Najean 1991	73	76	5	14	28.5%	43.80 [8.93, 214.79]
Navez 2015	48	50	8	9	20.7%	3.00 [0.24, 37.08]
Palandri 2014	50	52	5	10	25.9%	25.00 [3.82, 163.83]
Rossi 2002	14	18	5	7	25.0%	1.40 [0.19, 10.15]
Total (95% CI)		**196**		**40**	**100.0%**	**9.21 [1.70, 49.99]**
Total events	185		23			

Heterogeneity: Tau² = 1.96; Chi² = 8.97, df = 3 (P = 0.03); I² = 67%
Test for overall effect: Z = 2.57 (P = 0.01)

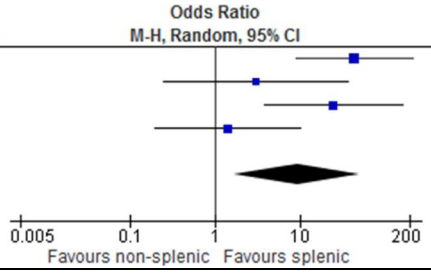


table with patient characteristics per sequestration group. Therefore, we were unable to assess the effect of possible confounders on the association. Furthermore, no studies performed multivariable adjustment for possible confounders.

Second, the decision to perform a splenectomy in patients was probably influenced by outcome of the sequestration scintigraphy. The included studies showed that patients with a Splenic sequestration pattern were more likely to get a splenectomy compared to patients with a Hepatic pattern. This might result in a selection bias for the pooled analyses, were only patients with a splenectomy were included. Furthermore, most included studies did not report data on the follow-up of the non-splenectomised patients. Future research should investigate both the splenectomised and non-splenectomised patients.

Third, definitions for both the sequestration pattern groups and outcome variables varied substantially between the studies. Therefore, a sensitivity analysis was performed using only studies with well defined independent and dependent variables, which showed similar results compared to the main analysis.

4.2. Clinical relevance

Current guidelines recommend splenectomy as a second or third line treatment for patients who have failed corticosteroid, Rituximab or TPO-RA therapy. Second-line medicinal therapies are often preferred over splenectomy in ITP patients. However, the long-term efficacy of many drug-based second-line treatments remains unclear, with many patients requiring a life-long continuation of medicinal therapy. (Bylsma et al., 2019; Grace and Neunert, 2016) Splenectomy may still be a cost-effective therapy for ITP patients with long-term (medicine-free) remissions in 60–70%. (Chaturvedi et al., 2018; Ghanima et al., 2012) On the other hand, a considerable portion of patients fail to show a post-splenectomy platelet response, while laparoscopic splenectomy has considerable short- and long-term complications. (Sarpatwari et al., 2010) Therefore, a reliable individual predictor-tool for post-splenectomy platelet response would be of great relevance for the management of ITP.

5. Conclusions

This systematic review and meta-analysis show that patients with a Splenic pattern show better post-splenectomy outcomes compared to patients with a Mixed or Hepatic pattern, with an odds ratio of 14 [4–55]. Whilst a randomized trial would be preferred for this research question, such a study design seems not ethical nor feasible. Given these limitations, this study suggests that it might be beneficial to select patients for splenectomy based on their sequestration pattern.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.103040.

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