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Immune thrombocytopenia: exploring antibodies, scintigraphy and immune modulation. Moving towards a new era for patients with ITP

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Chapter 5

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

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Abstract

Background 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.

Methods 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.

Results 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.

Conclusion 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.

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. (Sarpawari et al., 2010) None of these predictors are widely implemented in clinical practice, partly due to heterogenous study results. (Kojouri et al., 2004; Sarpawari 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 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; Sarpawari et al., 2010;

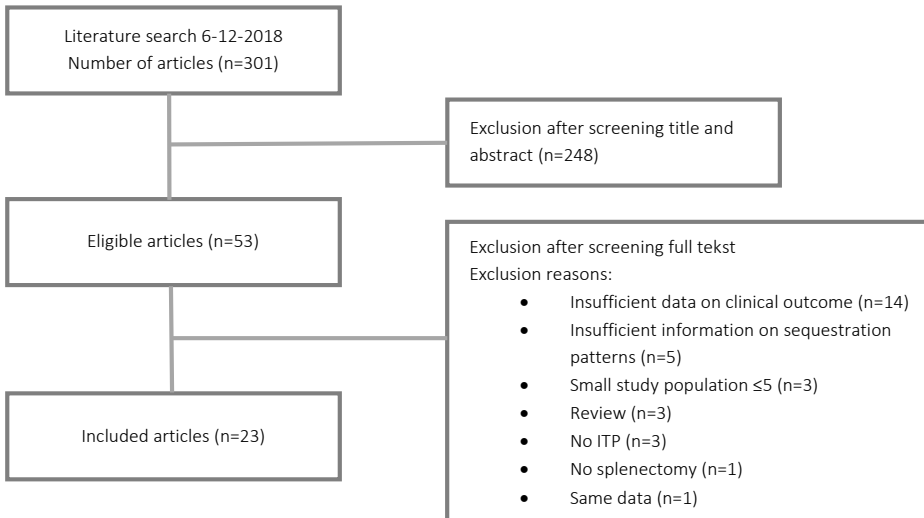
Richards and Thompson, 1979) Apart from a mini-review published in 2010, no systematic review or meta-analysis has been performed. (Cuker and Cines, 2010) This study aims to systematically review and meta-analyse the association between sequestration patterns and platelet response after splenectomy in ITP patients.

Methods

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 be 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.

Figure 1. Search strategy



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.

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.

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.

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, 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.

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.

Results

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.

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 $35 \times 10^9/L$ ($n = 18$ 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.

Table 1 – Characteristics of included studies

First author	Year	Country	ITP patients (n)	M (%)	Age (mean)	Platelet count [#]	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	–	Both	–	–	–	181 (100 %)	5	8
Gernsheimer	1989	USA & Can.	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.

platelet count $\times 10^9/L$

§ Isotope used, Chromium or Indium or both

The mean postoperative platelet count was $324 \times 10^9/L$, 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.

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).

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 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**.

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).

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.

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 (88.8%)	10 (5.6%)	10 (5.6%)
Non-splenic	51	26 (51.0%)	10 (19.6%)	15 (29.4%)

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.

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

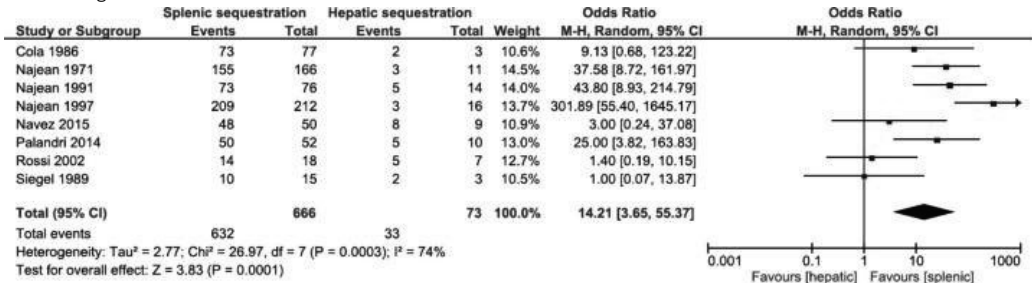
frequently seen in patients with Splenic sequestration (88.8 %) versus patients with a non-Splenic sequestration (51.0 %). The response rate (PR or NR) could not be determined in 5.6 % (10/180) of the patients with a Splenic and in 29.4 % (15/51) of the patients with a non-Splenic sequestration.

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

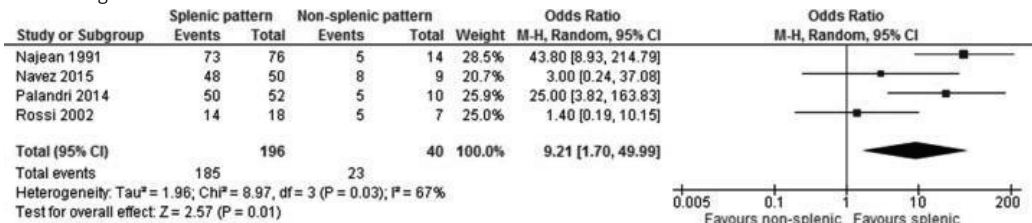
Eight studies provided data on post-splenectomy response rates that were stratified by sequestration pattern. These studies were eligible for pooled analysis. The Odds Ratio (OR) for a treatment response for the Splenic sequestration pattern was 14.21 [95 % CI 3.65,55.37] compared to the Hepatic sequestration pattern, with a substantial heterogeneity between the studies (I2 of 74 %), as shown in **Table 3a**. 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 I2 of 67 %, as shown in **Table 3b**. 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 3 – Pooled analysis and Forest Plot on the association between sequestration pattern and post-splenectomy platelet response.

a. Including all 8 studies



b. Including 4 studies with well-defined definitions



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.

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 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, where 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.

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. (Sarpawari et al., 2010) Therefore, a reliable individual predictor-tool for post-splenectomy platelet response would be of great relevance for the management of ITP.

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.

References

1. U. Abadi, O. Yarchovsky-Dolberg, M.H. Ellis., Immune thrombocytopenia: recent progress in pathophysiology and treatment. *Clin. Appl. Thromb. Hemost.*, 21 (5) (2015), pp. 397-404
2. Ahmed et al., Long-term outcome following splenectomy for chronic and persistent immune thrombocytopenia (ITP) in adults and children : splenectomy in ITP. *Ann. Hematol.*, 95 (9) (2016), pp. 1429-1434
3. Aslam et al., Splenic lymphocyte subtypes in immune thrombocytopenia: increased presence of a subtype of B-regulatory cells. *Br. J. Haematol.*, 173 (1) (2016), pp. 159-160
4. L.C. Bylsma, et al. Systematic literature review of treatments used for adult immune thrombocytopenia in the second-line setting. *Am. J. Hematol.*, 94 (1) (2019), pp. 118-132
5. S. Chaturvedi, D.M. Arnold, K.R. McCrae. Splenectomy for immune thrombocytopenia: down but not out. *Blood*, 131 (11) (2018), pp. 1172-1182
6. A. Cuker, D.B. Cines. Evidence-based mini-review: is indium-labeled autologous platelet scanning predictive of response to splenectomy in patients with chronic immune thrombocytopenia? *ASH Education Program Book*, 2010 (1) (2010), pp. 385-386
7. B.S. GA Wells, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute (2019)
8. W. Ghanima, et al. How I treat immune thrombocytopenia: the choice between splenectomy or a medical therapy as a second-line treatment *Blood*, 120 (5) (2012), pp. 960-969
9. R.F. Grace, C. Neunert. Second-line therapies in immune thrombocytopenia. *Hematology Am. Soc. Hematol. Educ. Program*, 2016 (1) (2016), pp. 698-706
10. Gugliotta, et al. Chronic idiopathic thrombocytopenic purpura (ITP): site of platelet sequestration and results of splenectomy. A study of 197 patients. *Scand. J. Haematol.* (407-12) (1981), Article 7199755, 10.1111/j.1600-0609.1981.tb01682.x
11. H. Kashiwagi, Y. Tomiyama. Pathophysiology and management of primary immune thrombocytopenia. *Int. J. Hematol.*, 98 (1) (2013), pp. 24-33
12. S. Kazi, et al. Autologous 111In-labelled platelet scan as a predictor of splenectomy outcome in ITP. *Br. J. Haematol.*, 184 (6) (2019), pp. 1043-1045
13. K. Kojouri, et al. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. *Blood*, 104 (9) (2004), pp. 2623-2634
14. M.P. Lambert, T.B. Gernsheimer. Clinical updates in adult immune thrombocytopenia. *Blood*, 129 (21) (2017), pp. 2829-2835
15. G. Leone, E. Pizzigallo. Bacterial infections following splenectomy for malignant and nonmalignant hematologic diseases. *Mediterr. J. Hematol. Infect. Dis.*, 7 (1) (2015), p. e2015057
16. E.P. Misiakos, et al. Laparoscopic splenectomy: current concepts. *World J. Gastrointest. Endosc.*, 9 (9) (2017), pp. 428-437
17. Najean, et al. The sequestration site of platelets in idiopathic thrombocytopenic purpura: its correlation with the results of splenectomy. *Br. J. Haematol.* (1971), 10.1111/j.1365-2141.1971.tb03425.x
18. Najean, et al. The site of platelet destruction in thrombocytopenic purpura as a predictive index of the efficacy of splenectomy. *Br. J. Haematol.* (1991), 10.1111/j.1365-2141.1991.tb04532.x
19. Y. Najean, J.D. Rain, C. Billotey. The site of destruction of autologous 111In-labelled platelets and the efficiency of splenectomy in children and adults with idiopathic thrombocytopenic purpura: a study of 578 patients with 268 splenectomies. *Br. J. Haematol.*, 97 (3) (1997), pp. 547-550
20. J. Navez, et al. Does the site of platelet sequestration predict the response to splenectomy in adult patients with immune thrombocytopenic purpura? *Platelets*, 26 (6) (2015), pp. 573-576
21. C. Neunert, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*, 117 (16) (2011), pp. 4190-4207
22. F. Palandri, et al. The choice of second-line therapy in steroid-resistant immune thrombocytopenia: role of platelet kinetics in a single-centre long-term study. *Am. J. Hematol.*, 89 (11) (2014), pp. 1047-1050
23. Quality Assessment, 2018 Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group. (2018)
24. J.D. Richards, D.S. Thompson. Assessment of thrombocytopenic patients for splenectomy. *J. Clin. Pathol.*, 32 (12) (1979), pp. 1248-1252
25. E. Rijcken, et al. Laparoscopic splenectomy for medically refractory immune thrombocytopenia (ITP): a retrospective cohort study on longtime response predicting factors based on consensus criteria. *Int. J. Surg.*, 12 (12) (2014), pp. 1428-1433
26. Rossi, et al. Platelet kinetic study in patients with idiopathic thrombocytopenic purpura (ITP) refractory or relapsing after corticosteroid treatment. *Hematol. J.* (2002), 10.1038/sj.thj.6200170

27. S.G. Sandler. The spleen and splenectomy in immune (idiopathic) thrombocytopenic purpura. *Semin. Hematol.*, 37 (1 Suppl 1) (2000), pp. 10-12
28. A. Sarpatwari, et al. Autologous 111 in-labelled platelet sequestration studies in patients with primary immune thrombocytopenia (ITP) prior to splenectomy: a report from the United Kingdom ITP Registry. *Br. J. Haematol.*, 151 (5) (2010), pp. 477-487
29. L. Tastaldi, et al. Laparoscopic splenectomy for immune thrombocytopenia (ITP): long-term outcomes of a modern cohort. *Surg. Endosc.*, 33 (2) (2019), pp. 475-485
30. H.L. Taylor, P. Whitley, A. Heaton. A historical perspective on platelet radiolabeling techniques. *Transfusion*, 46 (2006), pp. 53S-58S
31. N. Vianelli, et al. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. *Haematologica*, 90 (1) (2005), pp. 72-77

	Purpura".ti,ab OR "Immune Thrombocytopaenia".ti,ab OR "Autoimmune Thrombocytopaenia".ti,ab OR "Autoimmune Thrombocytopaenic Purpura".ti,ab)) AND (english.la OR dutch.la OR german.la OR french.la OR italian.la)		
Web of Science	TS=(((("Spleen" OR "Spleen Disease" OR "spleen" OR spleen* OR "splenic" OR splenic*) AND ("Radiodiagnosis" OR "imaging" OR radiogr* OR radiol* OR tomograph* OR scan* OR nuclear* OR radionuclid* OR "MRI" OR "magnetic resonance" OR mr imag* OR "radioisotope diagnosis" OR "Indium 111" OR "Indium-111" OR "Indium 111" OR "Indium111" OR "Indium" OR "indium" OR indium* OR "Chromium" OR "Radioisotope" OR "Chromium 51" OR "chromium" OR chromium* OR "Radioisotope" OR "111 In-labelled" OR "111In labelled" OR "111 In" OR "111In" OR "111 Indium" OR "111Indium")) AND ("immune thrombocytopenia" OR "immune thrombocytopaenia" OR immune thrombocytopeni* OR immune thrombocytopaeni* OR ("ITP" AND (purpura* OR thrombocyt*)) OR "idiopathic thrombocytopenic purpura" OR "Idiopathic Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopenic Purpuras" OR "Immune Thrombocytopenic Purpura" OR "Immune Thrombocytopenia" OR "Immune Thrombocytopenias" OR "Werlhof Disease" OR "Werlhof's Disease" OR "Autoimmune Thrombocytopenia" OR "Autoimmune Thrombocytopenias" OR "Autoimmune Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenic Purpura")) AND la=(english OR dutch OR german OR french OR italian)	107	38
		[0 meeting abstracts]	[0 meeting abstracts]
Cochrane Library	((("Spleen" OR "Spleen Disease" OR "spleen" OR spleen* OR "splenic" OR splenic*) AND ("Radiodiagnosis" OR "imaging" OR radiogr* OR radiol* OR tomograph* OR scan* OR nuclear* OR radionuclid* OR "MRI" OR "magnetic resonance" OR mr imag* OR "radioisotope diagnosis" OR "Indium 111" OR "Indium-111" OR "Indium 111" OR "Indium111" OR "Indium" OR "indium" OR indium* OR "Chromium" OR "Radioisotope" OR "Chromium 51" OR "chromium" OR chromium* OR "Radioisotope" OR "111 In-labelled" OR "111In labelled" OR "111 In" OR "111In" OR "111 Indium" OR "111Indium")) AND ("immune thrombocytopenia" OR "immune thrombocytopaenia" OR immune thrombocytopeni* OR immune thrombocytopaeni* OR ("ITP" AND (purpura* OR thrombocyt*)) OR "idiopathic thrombocytopenic purpura" OR "Idiopathic Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopenic Purpuras" OR "Immune Thrombocytopenic Purpura" OR "Immune Thrombocytopenia" OR "Immune Thrombocytopenias" OR "Werlhof Disease" OR "Werlhof's Disease" OR "Autoimmune Thrombocytopenia" OR "Autoimmune Thrombocytopenias" OR "Autoimmune Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenic Purpura")):ti,ab,kw AND la=(english OR dutch OR german OR french OR italian)	2	1
		[0 meeting abstracts]	[0 meeting abstracts]
Emcare	((exp *"Spleen"/ OR exp *"Spleen Disease"/ OR "spleen".ti,ab OR spleen*.ti,ab OR "splenic".ti,ab OR splenic*.ti,ab) AND (*("Radiodiagnosis"/ OR "imaging".ti,ab OR radiogr*.ti,ab OR radiol*.ti,ab OR tomograph*.ti,ab OR scan*.ti,ab OR nuclear*.ti,ab OR radionuclid*.ti,ab OR "MRI".ti,ab OR "magnetic resonance".ti,ab OR mr imag*.ti,ab OR exp *"radioisotope diagnosis"/ OR *"Indium 111"/ OR "Indium-111".ti,ab OR "Indium 111".ti,ab OR "Indium111".ti,ab OR *"Indium"/ OR "indium".ti,ab OR indium*.ti,ab OR *"Chromium"/ OR *"Chromium 51"/ OR "chromium".ti,ab OR chromium*.ti,ab OR exp *"Radioisotope"/ OR "111 In-labelled".mp OR "111In labelled".mp OR "111 In".mp OR "111In".mp OR "111 Indium".mp OR "111Indium".mp) AND ("immune thrombocytopenia".ti,ab OR "immune thrombocytopaenia".ti,ab OR immune thrombocytopeni*.ti,ab OR immune thrombocytopaeni*.ti,ab OR ("ITP".ti,ab AND (purpura*.ti,ab OR thrombocyt*.ti,ab)) OR "idiopathic thrombocytopenic purpura"/ OR "Idiopathic Thrombocytopenic Purpura".ti,ab OR "Idiopathic Thrombocytopenic Purpuras".ti,ab OR "Immune Thrombocytopenic Purpura".ti,ab OR "Immune Thrombocytopenia".ti,ab OR "Immune Thrombocytopenias".ti,ab OR "Werlhof	38	4

spleen* OR "splenic" OR splenic*) AND ("Radiodiagnosis" OR "imaging" OR radiogr* OR radiol* OR tomograph* OR scan* OR nuclear* OR radionuclid* OR "MRI" OR "magnetic resonance" OR mr imag* OR "radioisotope diagnosis" OR "Indium 111" OR "Indium-111" OR "Indium 111" OR "Indium111" OR "Indium" OR "indium" OR indium* OR "Chromium" OR "Radioisotope" OR "Chromium 51" OR "chromium" OR chromium* OR "Radioisotope" OR "111 In-labelled" OR "111In labelled" OR "111 In" OR "111In" OR "111 Indium" OR "111Indium") AND ("immune thrombocytopenia" OR "immune thrombocytopaenia" OR immune thrombocytopeni* OR immune thrombocytopaeni* OR "idiopathic thrombocytopenic purpura" OR "Idiopathic Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopenic Purpuras" OR "Immune Thrombocytopenic Purpura" OR "Immune Thrombocytopenia" OR "Immune Thrombocytopenias" OR "Werlhof Disease" OR "Werlhof's Disease" OR "Autoimmune Thrombocytopenia" OR "Autoimmune Thrombocytopenias" OR "Autoimmune Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenic Purpura"))

ScienceDirect	TITLE-ABSTR-KEY(("spleen" OR spleen* OR "splenic" OR splenic*) AND ("Radiodiagnosis" OR "imaging" OR radiogr* OR radiol* OR tomograph* OR scan* OR nuclear* OR radionuclid* OR "MRI" OR "magnetic resonance" OR mr imag* OR "radioisotope diagnosis" OR "Indium 111" OR "Indium-111" OR "Indium 111" OR "Indium111" OR "Indium" OR "indium" OR indium* OR "Chromium" OR "Radioisotope" OR "Chromium 51" OR "chromium" OR chromium* OR "Radioisotope") AND ("immune thrombocytopenia" OR "immune thrombocytopaenia" OR immune thrombocytopeni* OR immune thrombocytopaeni* OR "idiopathic thrombocytopenic purpura" OR "Idiopathic Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopenic Purpuras" OR "Immune Thrombocytopenic Purpura" OR "Immune Thrombocytopenia" OR "Immune Thrombocytopenias" OR "Werlhof Disease" OR "Werlhof's Disease" OR "Autoimmune Thrombocytopenia" OR "Autoimmune Thrombocytopenias" OR "Autoimmune Thrombocytopenic Purpura" OR "Idiopathic Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenic Purpura" OR "Immune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenia" OR "Autoimmune Thrombocytopaenic Purpura"))	2	1
Total		557	301

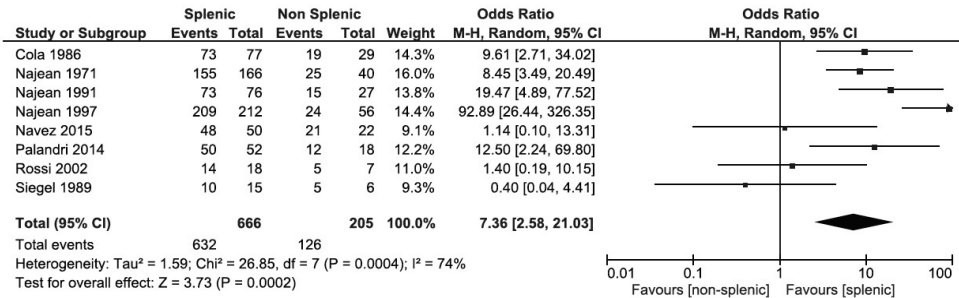
Supplementary table 2: Definition of sequestration pattern and post-splenectomy platelet response

First Author	Year	Definition of sequestration pattern	Definition of post-splenectomy platelet response
Aster	1969	Not reported; final S: L ratio is given Not reported; counts are measured from anterior precordium, and anterior and posterior liver and spleen. Divided in progressive splenic, progressive splenic and hepatic and immediate splenic, but no definition is given.	CR: restoration to normal levels. No definition PR/ NR
Ries	1974		CR: >150, PR: 90-150, NR: <50
Richard s	1979	Not reported; spleen/heart ratio is given Site of sequestration based on the ratio of surface radioactivity between spleen, liver and precordium. Splenic: S/P > 2.9, L/P < 1.5, spleno-hepatic: S/P > 2.9, L/P > 1.5, hepatic: S/P < 2.9, L/P > 1.5, diffuse: S/P < 2.9, L/P < 1.5	Not reported
Gugliotta	1981		CR: > 150, PR: 80-149, NR: <80
Heyns	1982	Site of sequestration based on major region of radioactivity (in %)	Not reported, PC are shown
Bought on	1985	Splenic uptake 20 min and 24 hours is measured.	Not reported, PC are shown
Cola	1986	Not reported	CR: >150, PR: 80-150 without symptoms, NR: <80
Gietz	1988	Splenic: S/L > 1.5, Mixed: S/L 1.0-1.5, Hepatic: S/L < 1.0	CR: > 150, PR: >80, medium response: 50-78, NR: <50
Fenaux	1989	Predominantly splenic: S/L > 1, Predominantly hepatic: S/L < 1.	Response >100, non-response <100 at 3 months after splenectomy
Gernsheimer	1989	Not reported	Successful response: > 100
Siegel	1989	Splenic: S/L > 1.2, Hepatic: S/L < 0.8, Mixed: S/L 0.8-1.2.	Not reported, PC are shown
Najejan	1971	Not reported; referred to Najejan 1967 Purely splenic: S/L ratio increased with >2.0 times between 30th minute and the time at which 90 % of the platelet initially circulating were destroyed. Predominant splenic: ratio increased by 1.4-2.0, mixed sequestration: ratio increased by 0.8-1.3, hepatic: ratio increased by <0.8	Not reported
Najejan	1991		CR: excellent response (>300), moderate response (100-300), PR: 50-100, NR: <50
Lamy	1993	Splenic: S > 1.2, Hepatic: L > 1.2, Mixed: S and L > 1.2, Normal: S and L: 1 ± 0.2. S= ratio splenic sequestration last day/ after 30 min and L= ratio hepatic sequestration last day/ after 30 min.	CR: >150, PR: 50-150, NR: <50
Najejan	1997	Same as Najejan 1991	Not reported
Louwes	1999	Not reported; splenic sequestration in baseline	Not reported Respons: PC >50 and an increase of >20 without medication, Non-response: PC <50 X10 ⁹ without medication
Uchida	2000	Not reported; mean spleen/ liver ratio is given	
Rossi	2002	Not reported; the ratio of maximum increase in splenic platelet uptake (SplPUpl) and liver platelet uptake (HepPUpl) is analysed	CR: >100, PR: 50-100, NR: <50

Sarpatwari	2010	Purely splenic: S/L > 2.0, predominantly splenic: S/L 1.4-2.0, mixed S/L 0.8-1.4 and hepatic S/L < 0.8	CR: PC >100 at 1-3 mo/ 6-12 mo or PC >100 and non-treatment at last FU CR: > 100 and no bleeding, PR: > 30 or 2x baseline PC and no bleeding, NR: <30 or less than 2x baseline PC or persistence of bleeding
Roca	2011	Not reported; mean S/H and L/H and S/L are reported	
Palandri	2014	Splenic: spleen/ heart: > 4.8, hepatic: liver/ heart > 8.0, diffuse: spleen/ heart > 4.8, liver/ heart > 8.0 and spleen/liver > 0.8	CR: >100, PR: 30-100, NR: <30
Navez	2015	Not reported The liver and spleen counts were calculated by the geometric mean method using a fixed region of interest for the anterior and posterior views. Positive uptake was defined as ratio >1.2	CR: > 100, PR: 30-100. NR: <30
Kazi	2018	(normal 0.8-1.2).	CR: >100 at 1-3 and 6-12 mo and >100 + non-reliance on treatment at last FU

Supplementary table 2: Pooled analysis and Forest Plot on the association between sequestration pattern and post-splenectomy platelet response using different sequestration grouping variables

a. Splenic vs. non-splenic



b. Hepatic vs. non-hepatic

