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RESEARCH

Efficacy and influencing factors of immunosuppressive therapy for pure red cell aplasia: meta-analysis and systematic review

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Abstract

Acquired pure red cell aplasia (aPRCA) is a rare hematological syndrome characterized by anemia and a significant reduction in erythroid progenitor cells. Immunosuppressive therapy (IST), including Corticosteroids (CS), Cyclosporine (CsA), and cyclophosphamide (CYC), is the primary treatment. However, variations in clinical efficacy and limited comparative studies have created uncertainty in therapeutic choices. This study aims to evaluate the efficacy of IST and the factors influencing treatment outcomes. A systematic search was conducted using PubMed, Embase, Cochrane Library, and Web of Science. Two researchers independently screened studies and extracted data. The quality of studies was assessed using the MINORS scale. Meta-analysis was performed using STATA/MP16, and effect size (ES) was calculated using fixed- or random-effects models based on heterogeneity. A total of 33 studies involving 1,193 patients were included. The overall efficacy of IST was significant, with a pooled ES of 0.656 (95% CI: 0.600–0.710). CsA demonstrated the highest efficacy (ES = 0.699; 95% CI: 0.615–0.779), followed by CYC (ES = 0.592; 95% CI: 0.423–0.752) and CS (ES = 0.568; 95% CI: 0.457–0.676). Subgroup analyses revealed that factors such as etiology, combination therapies, first- vs. second-line treatment, and genetic characteristics significantly influenced outcomes. Notably, the response to IST was higher in primary aPRCA (ES = 0.667; 95% CI: 0.598–0.733) compared to LGLL-associated (ES = 0.515; 95% CI: 0.393–0.637) and thymoma-associated (ES = 0.690; 95% CI: 0.492–0.864) aPRCA. The combination of CS and CsA yielded superior efficacy (ES = 0.761; 95% CI: 0.658–0.853) compared to combination of CS and CsA and monotherapy. First-line treatment demonstrated better efficacy than second-line treatment (ES = 0.659; 95% CI: 0.596–0.720) vs. (ES = 0.452; 95% CI: 0.199–0.715). The important finding was that (ES = 0.861; 95% CI: 0.595–1.000) in the STAT3 mutation (+) group and (ES = 0.375; 95% CI: 0.034–0.801) in the STAT3 mutation (-) group. IST demonstrates overall efficacy in aPRCA, with variations influenced by etiology, drug combinations, and genetic mutations such as STAT3. These findings highlight the need for personalized treatment strategies and further research to validate and optimize IST efficacy.

Keywords Pure red cell aplasia · Immunosuppressive therapy · Gene mutation · Meta-analysis

Introduction

aPRCA is a rare hematological syndrome defined by normocytic normochromic anemia, severe reticulocytopenia, and a marked reduction or absence of erythroid precursors in the bone marrow [1]. aPRCA can be classified as primary, idiopathic with no discernible cause, or secondary, associated with an underlying condition [2]. Primary aPRCA is an autoimmune disorder, which autoantibodies or other immune processes may mediate and where the targets of the autoantibodies may be on erythroid precursor cells, resulting in impaired erythroid differentiation [3]. Secondary aPRCA often occurs in the context of thymoma, large granular lymphocytic leukemia (LGLL), autoimmune or collagen vascular disorders, hematologic malignancies, or non-hematologic neoplasms [4]. The pathogenesis of secondary aPRCA is largely attributed to immune-mediated mechanisms, including cytotoxic lymphocyte-mediated suppression or autoantibody-mediated inhibition of erythropoiesis [5]. Secondary aPRCA may result from similar

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immune processes but is also influenced by the underlying disease [6]. Immunosuppressive therapy (IST) is the cornerstone of management for cases refractory to treating the primary disease [7]. The most commonly employed IST agents are corticosteroids (CS), cyclosporine (CsA), and cyclophosphamide (CYC). While these agents have demonstrated efficacy, substantial variability exists in clinical outcomes [3]. Additionally, previous studies investigating IST for aPRCA are predominantly retrospective, involve small sample sizes, and lack standardized treatment protocols. Consequently, the selection of therapeutic agents remains controversial, and treatment resistance or relapse is not uncommon. Recent research has indicated that underlying etiological characteristics, drug combinations, and genetic factors, particularly mutations in the STAT3 gene, may influence IST efficacy [8]. STAT3 mutations, frequently observed in LGLL-associated aPRCA, are believed to modulate immune dysregulation and contribute to IST resistance in certain cases. Despite these insights, the impact of such factors remains insufficiently studied due to the limited sample sizes and heterogeneity of existing data.

Given these challenges, this study aims to conduct a comprehensive meta-analysis and systematic review to evaluate the efficacy of IST in aPRCA. Additionally, we seek to identify and analyze the factors influencing treatment outcomes, such as etiology, genetic characteristics, and therapeutic strategies. The findings of this study are intended to provide evidence-based guidance for optimizing the clinical management of aPRCA.

Method

Search strategy and selection criteria

A systematic search was conducted in four electronic databases: PubMed, Embase, Cochrane Library, and Web of Science, covering literature up to March 31, 2024. The search was restricted to articles in English and used the following key terms: pure red cell aplasia, immunosuppressive treatment, corticosteroids (CS), cyclosporine (CsA), cyclophosphamide (CYC), and gene mutation. The detailed screening strategy is presented in Fig. 1. In addition, references from the included articles were manually searched to identify any relevant studies missed in the initial search.

Inclusion criteria

(1) Studies involving aPRCA patients, including both primary and secondary aPRCA. Excluded were studies on congenital pure red cell aplasia (e.g., Diamond-Blackfan anemia) and those involving specific etiologies such as pregnancy-associated aPRCA, ABO-incompatible stem cell transplantation-associated aPRCA, and infection-associated aPRCA, as these etiologies lead to distinct disease outcomes. (2) Clinical trials that investigated the efficacy of IST and its influencing factors in aPRCA patients. Treatment response data had to be extractable or calculable. (3) Only the study with the largest sample size was included

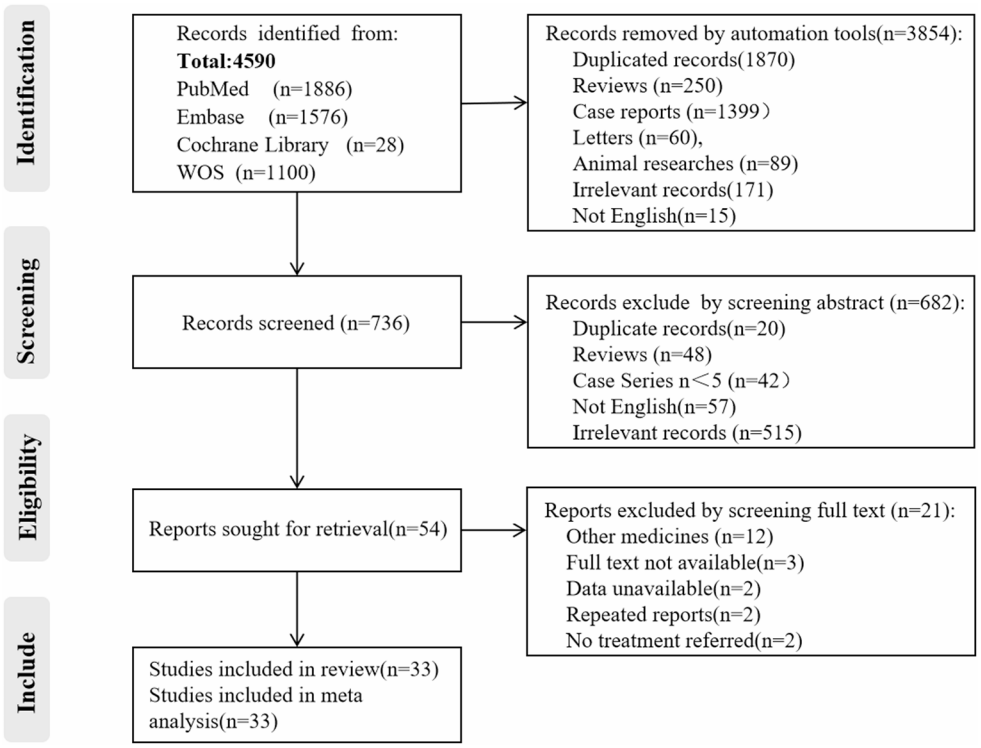

Fig. 1 Research flow chart of the meta-analysis

for studies conducted at the same center or during the same period.

Exclusion criteria

Case reports, case series ($n \leq 5$), comments, letters, reviews, animal studies, conference abstracts, and non-English articles were excluded.

Two independent investigators (Muyassar Yusup and JianPing Hao) performed the literature screening and data extraction. Discrepancies were resolved through discussion, and a third reviewer (GuangSheng He) was consulted if no consensus was reached. A total of 1,193 participants from 33 clinical studies met the inclusion criteria and were included in the final analysis [3, 9–40].

Data extraction and quality evaluation

Two researchers independently performed data extraction, with all extracted information cross-checked for accuracy. Any discrepancies were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted. Titles and abstracts were initially screened based on the inclusion criteria, followed by a full-text review to determine final eligibility. Data extraction included first author and year of publication, study design, sample size, patient demographics (age and sex), follow-up duration, etiology type, specific drugs and treatment regimens, number of patients responding positively to treatment, treatment outcomes, and study methodology (e.g., blinding, observational bias).

The included studies' quality and risk of bias were assessed using the Methodological Index for Non-Randomized Studies (MINORS) scale [41]. This tool evaluates study quality across 12 items: 8 methodological criteria and 4 additional criteria applicable to comparative studies. Each item was scored on a scale of 0 to 2, such as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) points. The evaluated methodological criteria included a clearly stated aim, the inclusion of consecutive patients, prospective data collection, appropriately defined endpoints, unbiased assessment of endpoints, admittance follow-up period, follow-up losses below 5%, and prospective sample size calculation. Given that none of the included studies had a control group, the 4 additional criteria for comparative studies were not applicable. Disagreements regarding quality assessment were resolved through discussion between two reviewers, with input from a third reviewer when necessary.

Statistical analysis

Meta-analysis was conducted using STATA/MP16 software. Heterogeneity among studies was assessed using the Cochran Q test and I^2 statistic. Heterogeneity was considered statistically significant if $I^2 > 50\%$ or the Q-test yielded $P < 0.1$. Given that the included studies were predominantly single-arm clinical trials, effect measurements were expressed as effect size (ES) with 95% confidence intervals (CI). A random-effects model was employed if significant heterogeneity was detected; otherwise, a fixed-effects model was applied. Subgroup analyses were performed to explore variations in IST efficacy based on etiology (primary vs. secondary aPRCA), type of medication (monotherapy or combination therapy), treatment line (first-line vs. second-line therapy), and genetic factors (STAT3 mutation status). Statistical significance was set at an alpha level (α) of 0.05. Publication bias was evaluated using Begg's and Egger's tests, with results indicating the presence or absence of bias.

Results

Included studies

A total of 4,590 citations were retrieved from the electronic database search. Studies were screened for relevance after the automatic removal of duplicates using literature management software. Excluded at this stage were reviews, case reports, animal studies, studies on other types of aPRCA, and non-English articles. This process yielded 736 potentially relevant citations for further abstract screening. Following the abstract screening, 682 records were excluded for reasons such as irrelevance to the study topic or not meeting the inclusion criteria. Full-text reviews were then conducted for the remaining studies, resulting in the exclusion of 21 additional studies due to the use of experimental medicines not within the scope of this study ($n = 12$), full text unavailable ($n = 3$), insufficient data for analysis ($n = 2$), duplicate reports ($n = 2$), no mention of treatment ($n = 2$). Ultimately, 33 studies met al.l inclusion criteria and were included in this meta-analysis and systematic review [3, 9–12, 15–17, 19–40]. A detailed overview of the selection process is presented in Fig. 1. This review and meta-analysis have been registered with the International Prospective Register of Systematic Reviews (INPLASY) under registration number INPLASY202440070.

Characteristics of included studies

33 studies involving 1,193 patients, conducted between 1994 and 2024, met the selection criteria. Among these,

two were prospective observational studies [3, 39], while the remainder were retrospective observational studies or case series. Notably, none of the included studies featured a control group. The study populations were predominantly Asian, with a smaller proportion comprising American and European participants. Detailed examination of the full texts and original data from the literature provided comprehensive demographic and clinical information. Extracted data included the number of patients receiving medication in each study, patient age and sex distribution, the total number of patients achieving remission, pathological subgroups (primary vs. secondary aPRCA), Specific immunosuppressive agents utilized in each group, the number of patients responding positively to treatment, additional details related to medication use and therapeutic strategies. This collated data facilitated robust subgroup analyses and informed the overall findings of this meta-analysis.

Irrelevant records

studies that did not pertain to aPRCA, such as those on Diamond-Blackfan anemia, PRCA caused by parvovirus B19 or other infections, PRCA following hematopoietic stem cell transplantation, erythropoietin-induced PRCA, or basic experimental research.

The main pathogenesis of aPRCA includes primary aPRCA, thymoma-associated aPRCA, large granular lymphocytic leukemia (LGLL)-associated aPRCA, autoimmune diseases, and other rare etiologies, such as abnormal cytogenetics, chronic lymphocytic leukemia (CLL), and drug-induced aPRCA [42]. Primary aPRCA constitutes most cases, followed by LGLL-associated and thymoma-associated aPRCA. Autoimmune disease-associated aPRCA is rare, with only 32 cases identified across the included studies [43, 44]. Immunosuppressive agents evaluated in this study included corticosteroids (CS; $n=245$), cyclosporine (CsA; $n=558$), and cyclophosphamide (CYC; $n=109$). Treatment effectiveness was defined as hemoglobin normalization and transfusion independence, encompassing partial and complete remission. Follow-up data were available for 26 studies, with a mean follow-up duration of 40.1 months. The quality of the included studies was rated as moderate based on the MINORS tool. Detailed information regarding the study characteristics and quality assessment is presented in Table 1.

Efficacy of IST for aPRCA

The overall response rate and the response rates for individual immunosuppressive agents were calculated by synthesizing data from 33 studies. Effectiveness rates for each drug were pooled based on their usage in the included studies.

The overall response rate of IST in the general population

Data from 33 studies reporting the effectiveness of IST in treating aPRCA were analyzed. Significant heterogeneity was observed among the included studies ($I^2=62.69\%$, $P=0.00$). Consequently, a random-effects model was applied, as illustrated in Fig. 2. The pooled ES was 0.656 (95% CI: 0.660–0.710), with $Z=29.233$, $P=0.00$, indicating statistically significant effectiveness. This result suggests that IST achieves an overall response rate of 65.6% in aPRCA patients. Publication bias was assessed using Begg's and Egger's tests, yielding $P=0.566$ and $P=0.775$, respectively. These results indicate that the likelihood of significant publication bias in this analysis is minimal.

Efficacy of individual immunosuppressive agents

The treatment efficacy of individual immunosuppressive drugs was analyzed by extracting data on treatment response rates from the included studies. Corticosteroid (CS) monotherapy was relatively uncommon and primarily administered with cyclosporine (CsA). Subgroup analyses were performed using data from monotherapy groups to assess the distinct efficacies of cyclosporine and corticosteroids. Heterogeneity testing was conducted for each subgroup, with overall ($I^2=60.621\%$, $P=0.000$), CS ($I^2=51.742\%$, $P=0.005$), CsA ($I^2=64.996\%$, $P=0.000$), and CYC ($I^2=44.954\%$, $P=0.035$), respectively. These results indicated statistically significant heterogeneity across the studies. Consequently, a random-effects model was employed for the meta-analysis (Fig. 3). The pooled *ES* for these trials was 0.639 (95% CI: 0.570–0.703), with $Z=23.926$, $P=0.000$, demonstrating significant efficacy. The individual ES values were as follows: *ES* for CS was 0.568 (95% CI: 0.457–0.676), $Z=13.208$, $P=0.000$; *ES* for CsA was 0.699 (95% CI: 0.615–0.779), $Z=19.761$, $P=0.000$; *ES* for CYC was 0.592 (95% CI: 0.423–0.752), $Z=8.903$, $P=0.000$. Begg's and Egger's tests were performed to assess publication bias. The *P*-values were 0.804 and 0.718, respectively, indicating no significant publication bias among the included studies.

Table 1 Characteristics of studies included in the systematic review and meta-analysis

Study	Design	Population								IST	Follow-up (mo)	first/second line	QA
		N	Age(M)	Sex(M%)	primary	TGLL	Thymoma	AID	Other				
Clark 1984 [9]	retrospective case series	27	42	51	22	4	1	0	0	CS	90.7	first and second	10
Means 1991 [3]	prospective observational study	9	42	56	NA	NA	NA	NA	NA	CsA	NA	second	12
Kwong 1996 [10]	retrospective case series	8	58	50	8	0	0	0	0	CS, CsA	37.6	first and second	10
Lacy 1996 [11]	retrospective observational study	35	63	NA	18	9	2	0	6	CS, CsA, CYC	54	first and second	10
Charles 1996 [12]	retrospective observational study	19	57	68	8	0	3	6	2	CS, CYC	43.9	first and second	11
Thompson 2006 [13]	retrospective observational study	13	63	54	0	0	13	0	0	CS, CsA	26	first	11
Sawada 2007 [14]	retrospective observational study	62	55	37	62	0	0	0	0	CS, CsA, CYC	54	first	11
Fujishima 2008 [15]	retrospective observational study	14	60	57	0	14	0	0	0	CS, CsA, CYC	90	first and second	11
Hirokawa 2008 [16]	retrospective observational study	41	66	43	0	0	41	0	0	CS, CsA, CYC	18	first and second	11
Malhotra 2008 [17]	retrospective case series	9	40	75	5	2	2	0	0	CS	22	first	10
Kawano 2013 [18]	retrospective case series	5	41	40	3	0	2	0	0	CS, CsA	78	first	10
Rivoisy 2016 [19]	retrospective observational study	11	57	36	0	0	11	0	0	CS, CsA, CYC	23	first and second	10
Peng 2016 [20]	retrospective case series	10	54	90	0	10	0	0	0	CYC	41	second	11
Chalayer 2017 [21]	retrospective observational study	8	36	0	0	0	0	8	0	CS	27	first	9
Shi 2017 [22]	retrospective case series	6	NA	NA	0	6	0	0	0	CYC	NA	first	11
Balasubramanian 2018 [23]	retrospective observational study	55	61	56	32	14	9	0	0	CsA, CYC	40	first	12
Fu 2018 [24]	retrospective observational study	41	NA	NA	24	1	5	3	8	CS, CsA	31	first	12
Fujishima 2018 [25]	retrospective observational study	103	NA	NA	52	5	16	NA	NA	CS, CsA, CYC	NA	first	8
Kawakami 2018 [26]	retrospective observational study	29	67	27	NA	NA	NA	NA	NA	CsA	NA	first	8
Moriyama 2018 [27]	retrospective observational study	8	59	62	0	0	8	0	0	CS, CsA	54.5	first	9
Wu 2018 [28]	retrospective observational study	42	56	48	20	10	5	2	5	CS, CsA	14.5	first	11
Wu 2019 [29]	retrospective observational study	79	56	42	52	11	10	2	4	CS, CsA	3	first	11
Liu 2020 [30]	retrospective observational study	69	61	46	43	14	6	0	6	CS, CsA	41	first	8
Long 2020 [31]	retrospective observational study	30	63	37	31	0	0	0	0	CS, CsA	8	first	11
Liu 2021 [32]	retrospective observational study	65	60	43	0	65	0	0	0	CS, CYC	10	first	12
Lobbes 2021 [33]	retrospective observational study	24	39	17	0	0	0	24	0	CS, CsA, CYC	76	first and second	11
Yen 2021 [34]	retrospective case series	7	NA	43	0	0	7	0	0	CS, CsA	56	first	10
Kawakami 2022 [35]	retrospective observational study	90	65	NA	26	36	15	8	5	CsA, CYC	NA	first and second	10
Salama 2022 [36]	retrospective observational study	13	72	85	0	13	0	0	0	CsA, CYC	80	first	12
Wu 2022 [37]	retrospective observational study	100	57	47	60	28	6	2	4	CS, CsA	NA	first	12
Park 2023 [38]	retrospective observational study	19	68	37	3	6	0	0	0	CS, CsA, CYC	NA	first	10
Yang 2023 [39]	prospective observational study	30	66	63	30	0	0	0	0	CsA	20	first	15
Yang 2024 [40]	retrospective observational study	112	64	53	62	NA	NA	NA	NA	CsA	3	first	12

AID: autoimmune disease; CS: corticosteroid; CsA: Cyclosporin A; CYC: cyclophosphamide; LGLL: large granular lymphocyte leukemia; N: number of patients; NA: not available; Other: Abnormal Cytogenetics, CLL, Drug-induced, etc. indicates studies excluded from the meta-analysis due to imprecise or inaccurate response criteria definitions. QA: quality assessment; mo: month

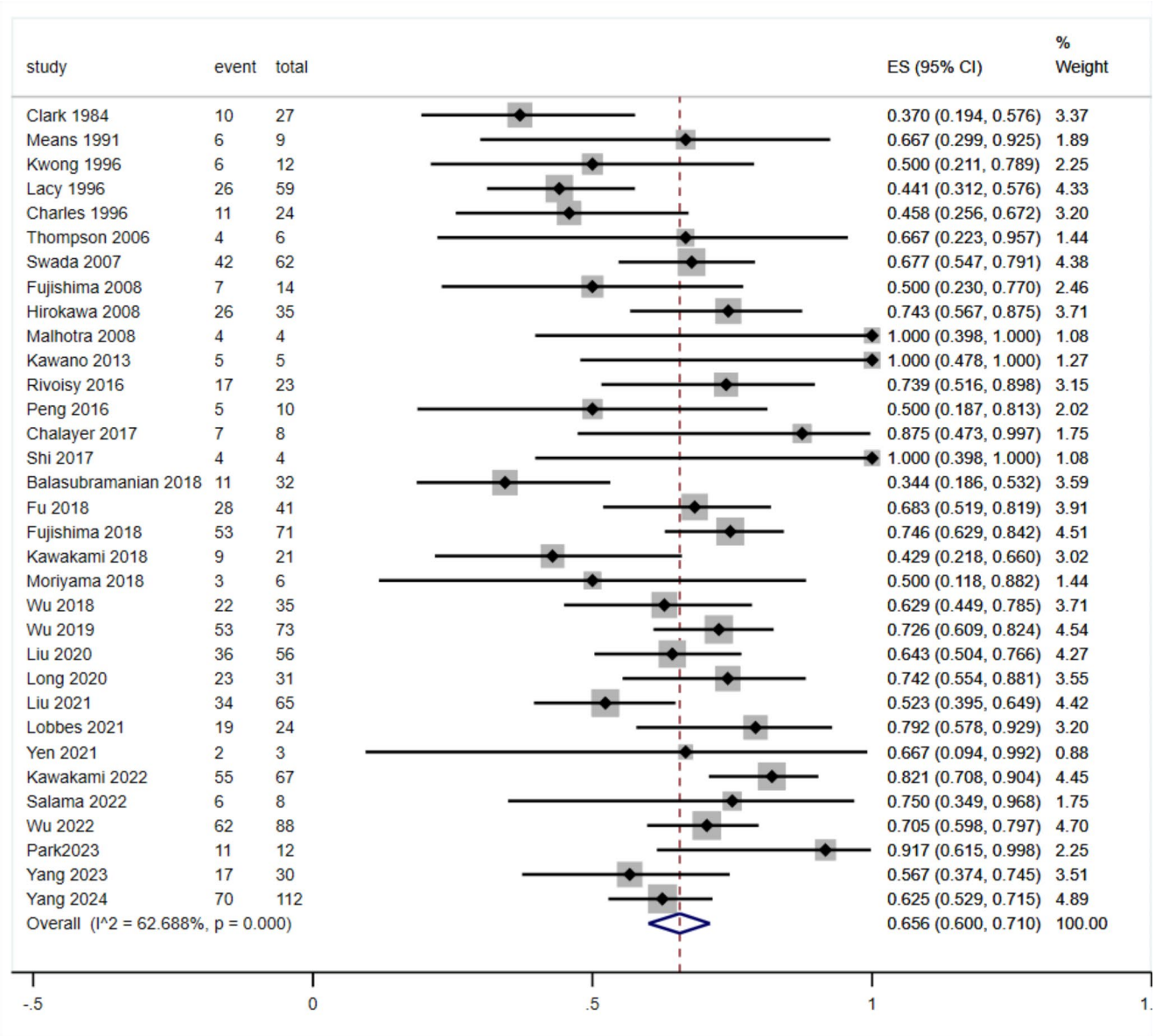

Fig. 2 Forest map of the overall response rate of IST in the overall population

Influencing factors of IST effects for aPRCA

The pathophysiological mechanism underlying aPRCA remains poorly understood, and the response to IST is often limited. Evidence from the PRCA2004/2006 study demonstrated that poor responses to immunosuppression and relapse anemia were significantly associated with increased mortality [14–17]. Previous aPRCA-related studies have attempted to find factors that influence efficacy. Wu 2018 et al. investigated clinical factors impacting IST efficacy and found that overall therapeutic efficacy was not significantly affected by age, etiology, reticulocyte count, or absolute lymphocyte count. However, females responded better to IST than males (P = 0.041). Additionally, univariate analysis indicated that initial therapy was associated with higher clinical efficacy [28]. Specifically, the combination of CsA with CS (P=0.009) and primary aPRCA (P=0.019) were identified as factors contributing to complete remission when compared with CS monotherapy and secondary aPRCA, respectively [29]. Beyond clinical factors, recent studies have highlighted the critical role of genetic mutations, particularly in the STAT3 gene, in influencing IST efficacy in aPRCA. STAT3 mutations have been correlated with differential response rates to IST. However, the small sample sizes of existing studies have resulted in discrepancies and a lack of definitive conclusions regarding the precise role of these mutations.

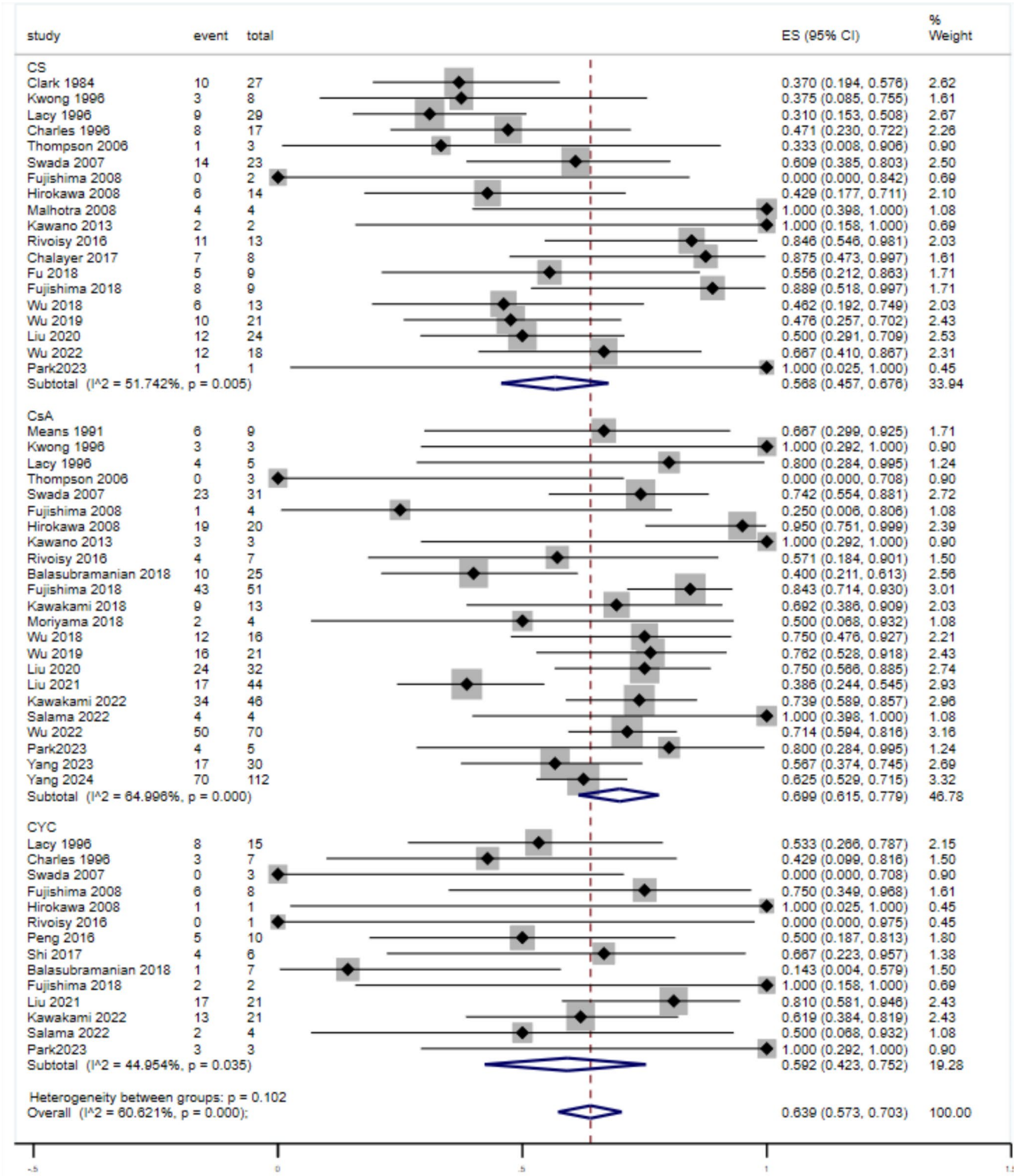

Fig. 3 Forest map of response rate of Individual immunosuppressive agents

Subgroup analyses were conducted to explore potential variations of IST efficiency among etiologic characteristics, monotherapy or combination IST, first- or second-line therapy, and specific gene mutations, providing further insights into the efficacy of IST in specific contexts.

The response rate of different etiology

The etiologic characteristics of the included studies were analyzed in subgroups, including primary, LGLL-associated, thymoma-associated, and AID-associated aPRCA.

The total result of the heterogeneity test is $I^2=48.308\%$ and $P=0.000$. Fifteen literature related to primary aPRCA were studied, and the result of the heterogeneity test was $I^2=40.511\%$ and $P=0.052$; eleven studies related to LGLL-associated aPRCA, the result of the heterogeneity test was $I^2=36.375\%$ and $P=0.108$; eleven studies related to Thymoma-associated aPRCA, the result of the heterogeneity test is $I^2=48.676\%$ and $P=0.035$. In two studies related to AID-associated aPRCA, the test results for heterogeneity between the two studies were not statistically significant. Based on the results of the heterogeneity test, it was concluded that there was heterogeneity among the included studies, so the effect sizes were combined using a random effects model.

Given the heterogeneity, effect sizes were calculated using a random-effects model. In the primary aPRCA subgroup, the use of IST was supported by the combined *ES* of 0.667(95% CI: 0.59–0.733), with a statistically significant change ($Z=23.590$, $P=0.000$). In LGLL associated aPRCA, $ES=0.515$(95% CI: 0.393–0.637) with ($Z=11.139$, $P=0.000$). In thymoma-associated aPRCA, $ES=0.690$(95% CI: 0.492–0.864) with ($Z=8.491$, $P=0.000$). In AID-associated aPRCA, $ES=0.819$(95% CI: 0.655–0.944) with ($Z=11.043$, $P=0.000$). These findings indicate that IST achieved response rates of 66.7%, 51.5%, 69.0%, and 81.9% in primary, LGLL-associated, thymoma-associated, and AID-associated aPRCA, respectively. The higher response rate observed in AID-associated aPRCA may suggest increased sensitivity to IST in this subgroup. Publication bias was assessed using Begg's ($P=0.628$) and Egger's ($P=0.434$), indicating no significant publication bias. Figure 4 illustrates the forest plots detailing the response rates for different etiologies.

The efficacy of each immunosuppressive agent, such as CS, CsA, and CYC, was analyzed across different etiological subgroups, including primary aPRCA, LGLL-associated aPRCA, and thymoma-associated aPRCA. Heterogeneity was statistically significant in the CS and CsA subgroups that applied a random-effects model, but no significant heterogeneity was observed in the CYC subgroup that applied a fixed-effects model. The efficiency results of CS for primary aPRCA, LGLL-associated aPRCA, and thymoma-associated aPRCA were 52.7%, 18.5%, and 57.2%. The efficiency results of CsA in each etiologic group were 77.5%, 56.4%, 85.2%. These findings demonstrate that CsA exhibited the highest efficacy across all etiological subgroups, particularly for thymoma-associated aPRCA (85.2%). In contrast, CYC showed moderate efficacy in LGLL-associated aPRCA but was ineffective for primary aPRCA in the limited data available. Publication bias was assessed for each drug subgroup using Begg's and Egger's tests. The results indicated no significant bias in the CS subgroup (Begg's test $P=0.870$, Egger's test $P=0.617$), CsA subgroup (Begg's test $P=0.607$, Egger's test $P=0.224$), and CYC subgroup(Begg's test $P=0.371$, Egger's test $P=0.178$). Figure 5 provides a detailed visualization of these results.

The response rate of multitherapy

The efficacy of combined immunosuppressive therapy (multitherapy) was analyzed using data from the included studies. Due to the limited number of studies available for this analysis, heterogeneity testing revealed minimal variability among the included studies. Consequently, a fixed-effects model was employed for the meta-analysis.

The efficacy of combined immunosuppressive therapy (multitherapy) was evaluated in the included studies. The analysis revealed that combination regimens demonstrated significantly higher efficacy compared to monotherapy. For instance, the efficacy rate of the combination of CS and CsA was significantly higher at 76.1%. In contrast, the efficacy rate of the combination of CS and CYC was 66.4%, with statistical significance. These results suggest that combination therapy provides a clear advantage over monotherapy regarding treatment outcomes, with the CS+CsA regimen showing the highest efficacy, as indicated in Fig. 6. Publication bias was assessed for the included studies with Begg's test $P=1.000$ and Egger's test $P=0.693$, and these results indicate that publication bias was not statistically significant.

The response rate of first-line and second-line therapy

The response rates of first-line and second-line IST were analyzed. Most patients in the included studies received IST as a first-line treatment. Due to statistically significant heterogeneity among the included studies ($I^2=54.492$, $P=0.00$), effect sizes were pooled using a random-effects model.

IST appears to be markedly effective for the aPRCA as first-line treatment for aPRCA, and the effective rate was 0.659 (95% CI: 0.598–0.720), ($I^2=54.492\%$, $P=0.000$) according to the random effects meta-analysis. There were

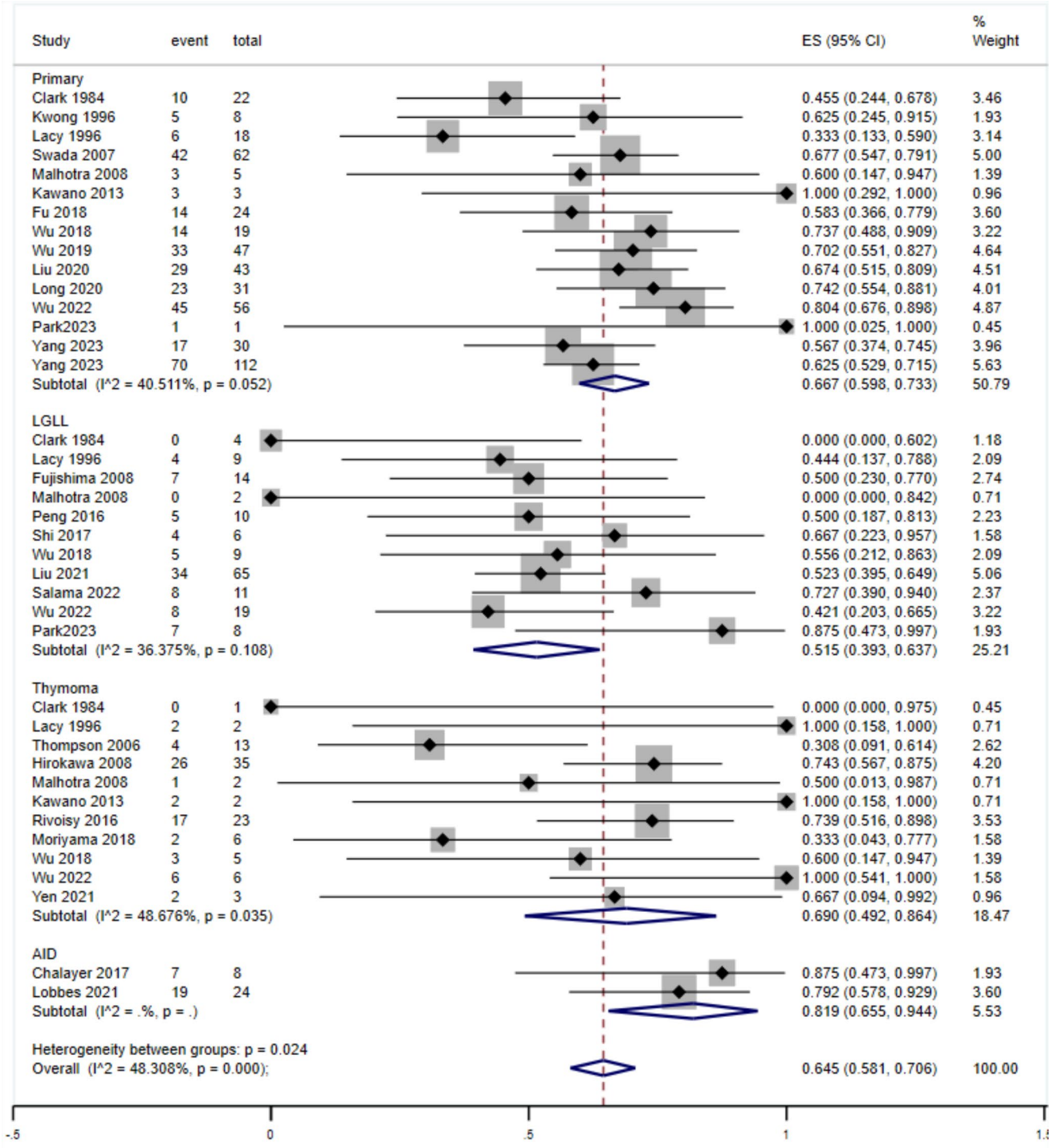

Fig. 4 Forest map of response rate according to different etiology

no significant differences in CS, CsA, and CYC effectiveness as first-line. The *ES* of CS was 0.624(95% CI: 0.526–0.727), (I^2 = 44.863%, P = 0.024) with 275 participants across 16 studies, the *ES* of CsA was 0.683(95% CI: 0.593–0.767), (I^2 = 63.462%, P = 0.000) with 478 participants across 17 studies, and the *ES* of CYC was 0.674(95% CI: 0.442–0.876), (I^2 = 54.543%, P = 0.040) with 64 participants across 7 studies. These findings suggest that IST, regardless of the specific agent used, is effective as a first-line therapy for aPRCA. Figure 7 provides detailed forest plots of the response rates for first-line therapies. Finally, the publication bias was assessed using Begg's (P = 0.484) and Egger's

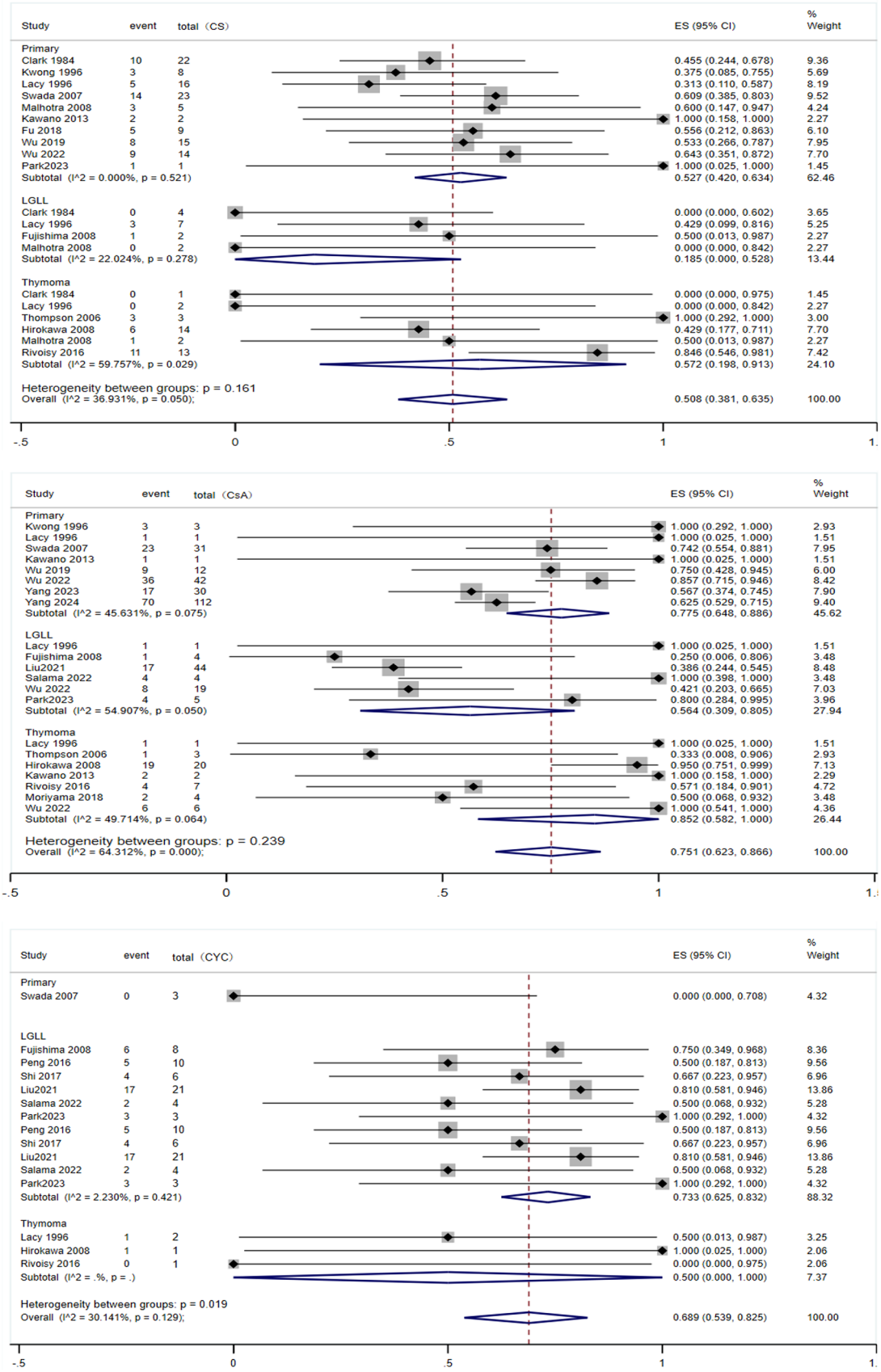

Fig. 5 Forest map of response rate according to Individual immunosuppressive agents in different etiology

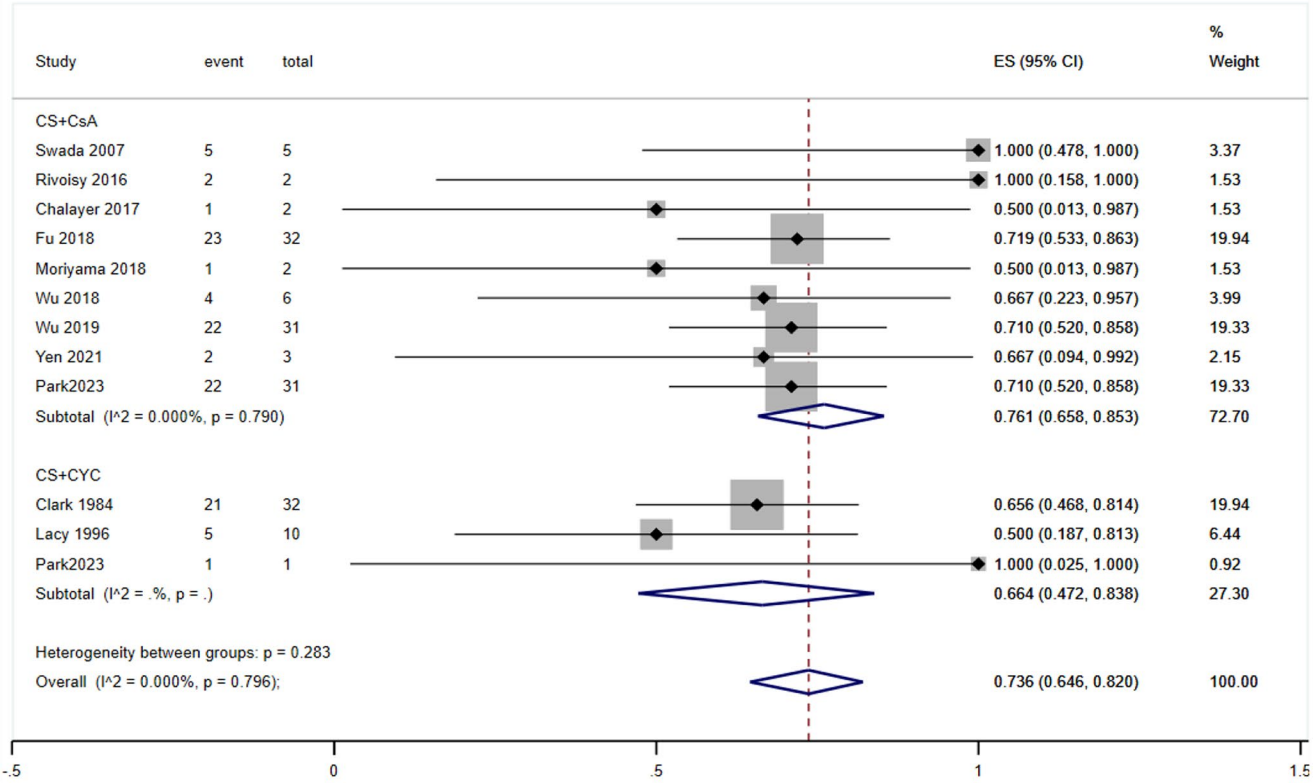

Fig. 6 Forest map of response rate of Response rate of multitherapy

($P=0.651$) tests. These results indicate no statistically significant publication bias among the included studies.

The use of IST as a second-line treatment for aPRCA was analyzed. Heterogeneity testing demonstrated significant variability among the included studies ($I^2=71.245\%$, $P=0.001$). Consequently, a random-effects model was employed for the meta-analysis. The combined *ES* was 0.452 (95% CI:0.199–0.715) with a statistically significant change ($P<0.05$). However, the substantial heterogeneity among the subgroup study ($I^2=0.000\%$; $P=0.000$) and the limited number of included studies suggest that the results should be interpreted cautiously. These findings may reflect the variability in patient populations and study methodologies rather than a definitive conclusion about IST efficacy in second-line settings. Publication bias was assessed using Begg's $P=0.711$ and Egger's $P=0.870$. These results indicate no statistically significant publication bias. Figure 8 provides detailed forest plots illustrating the response rates for second-line therapy.

Gene mutation

The current evidence demonstrates that aPRCA patients frequently exhibit genomic alterations, which may represent a significant risk factor for the disease [45]. Among these, mutations in the STAT3 gene are particularly notable, occurring in approximately 40% of patients with LGLL. Firstly, the SH2 dimerization and activation domain of STAT3 is frequently mutated in patients with LGLL [46]. Studies by Ishida et al. and Qiu et al. have found a strong correlation between STAT3 mutations and aPRCA in LGLL patients [47, 48]. Later investigations, including those by Balasubramanian (2018) and Kawakami (2018), extended these findings by identifying STAT3 mutations not only in LGLL-associated aPRCA but also in primary and thymoma-associated aPRCA [23, 26]. These findings suggest that STAT3-mutated CD8+T cells may contribute to the selective inhibition of erythroid progenitors, implicating aberrant STAT3 signaling as a central mechanism underlying aPRCA pathogenesis. In terms of disease pathogenesis, there are two potential mechanisms of unresponsiveness to immunosuppression: clonal changes in autoaggressive lymphocytes reacting against erythroid progenitors and clonal hematopoiesis by stem/progenitor cells that have undergone somatic mutations during the disease progression of aPRCA [49]. Regarding the former, mutations in the STAT3 were detected in 40% of patients with LGLL and have been found in aPRCA [46, 47]. On this theoretical foundation, several studies have analyzed the relationship between mutations in the STAT3 gene and response rates to IST. Kawakami 2018 recently reported that STAT3 mutation-positive patients were less responsive to CsA than those with wildtype STAT3.

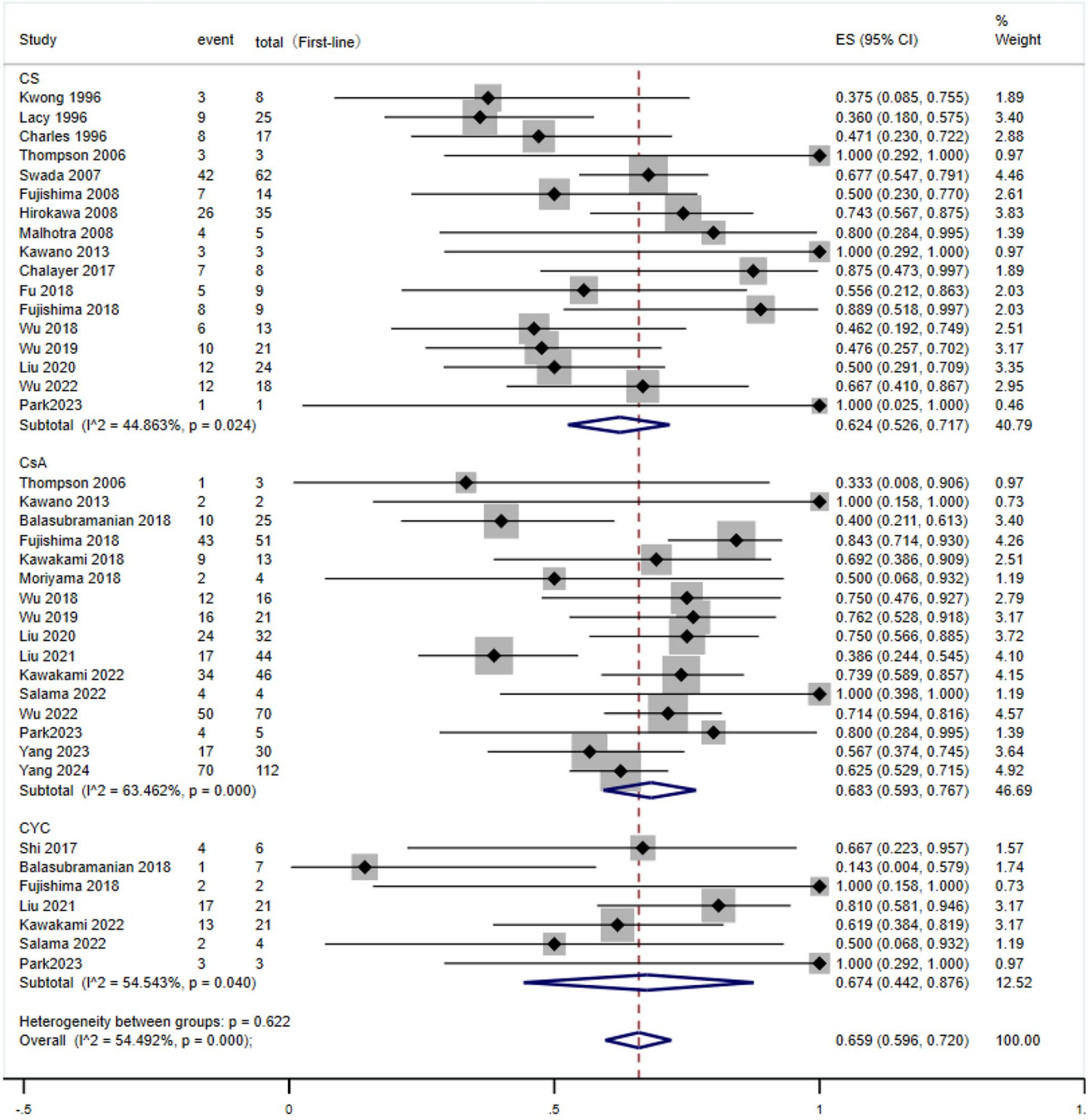

Fig. 7 Forest map of response rate of Individual immunosuppressive agents in first-line therapy

These results support the hypothesis that clonal changes in autoaggressive lymphocytes may be related to the refractoriness of aPRCA to immunosuppression. We study the outcomes of previously published attempts to study the STAT3 gene concerning the efficacy of IST. These results highlight the importance of STAT3 mutations in both the pathogenesis and treatment response of aPRCA. Further studies are needed to elucidate the precise role of STAT3 mutataion in erythroid progenitor suppression and to explore targeted therapeutic strategies for mutation-positive patients.

Among the included studies, seven examined the relationship between STAT3 mutations and IST treatment outcomes, with five studies providing quantitative data. Details of these studies are summarized in Table 2. A subgroup analysis compared treatment response rates in patients with and without STAT3 mutations. Due to significant heterogeneity ($I^2 = 79.012\%$, $P = 0.000$), the random-effects

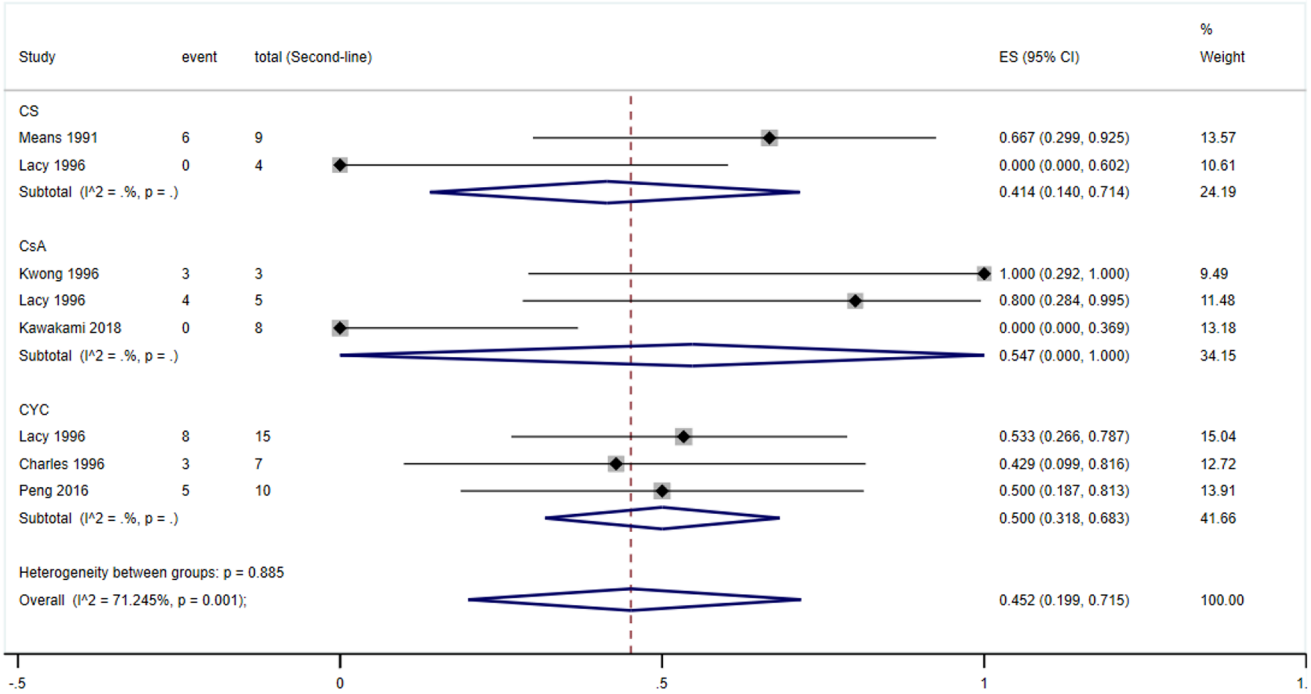

Fig. 8 Forest map of response rate of Individual immunosuppressive agents in second-line therapy

Table 2 Characteristics of studies associated with gene mutation and IST response

Study	STAT3 mutation(+)		STAT3 mutation(-)		IST
	total	response to IST	total	response to IST	
Kawakami 2018 [26]	13	9	8	0	CsA
Wu 2018 [28]	0	0	42	NA	CS, CsA
Liu 2021 [32]	14	NA	51	26	CsA, CYC
Kawakami 2022 [35]	41	NA	0	0	CsA, CYC
Salama 2022 [36]	0	0	8	6	CsA, CYC
Park 2023 [38]	4	4	0	0	CS, CsA, CYC
Yang 2023 [39]	2	2	0	0	CsA

*NA: detailed data unavailable

model was employed to estimate the pooled *ES* and the respective 95% CI. The results indicate a markedly higher response rate to IST in the STAT3 mutation-positive group (86.1%, *ES*=0.861, 95% CI: 0.595–1.000) compared to the mutation-negative group (37.5%, *ES*=0.375, 95% CI: 0.034–0.801). Furthermore, Begg's (P=0.181) and Egger's (P=0.496) regression tests were used to assess publication bias among the included studies, and both tests indicated no statistically significant publication bias among the included studies.

While detailed data on STAT3 mutation-related medication use or response rates were unavailable in some studies [28, 32, 35], findings suggest a differential response to specific drugs based on STAT3 mutational status. Patients with STAT3 mutations exhibited a significantly higher response rate to CYC than those without mutations (P=0.018). In contrast, the overall response rate to CsA did not differ significantly by the STAT3 mutational status (P=0.321) [35]. In a direct comparison, patients with STAT3 mutations appeared to respond better to CYC than to CsA (83.3% vs. 37.5%), though this difference was not statistically significant (P=0.138) [32]. These findings are depicted in Fig. 9. In addition to STAT3 mutations, other genetic factors influencing IST efficacy have been explored. Long et al. identified BCOR, BCORL1, CSMD1, JAK3, and RUNX1 as the most frequently mutated genes in aPRCA [31]. Subgroup analysis revealed that patients with BCOR or BCORL1 mutations had a similar response to IST compared to those without mutations (P=0.235) but showed a better response than those with other mutations (P=0.019) [31]. Zhang et al. utilized next-generation sequencing and identified FANCF and LRP1B mutations as potentially associated with aPRCA in four patients [50]. Fujishima et al. reported seven driver mutations in genes such as TET2, DNMT3A, and KDM6A across four aPRCA patients, with two patients carrying multiple mutations in TET2. Five patients exhibited mutations with high VAFs exceeding 0.3, suggesting clonal hematopoiesis as a potential factor in aPRCA pathophysiology [49]. Although studies like those by Fujishima et al. did not directly correlate these mutations with IST

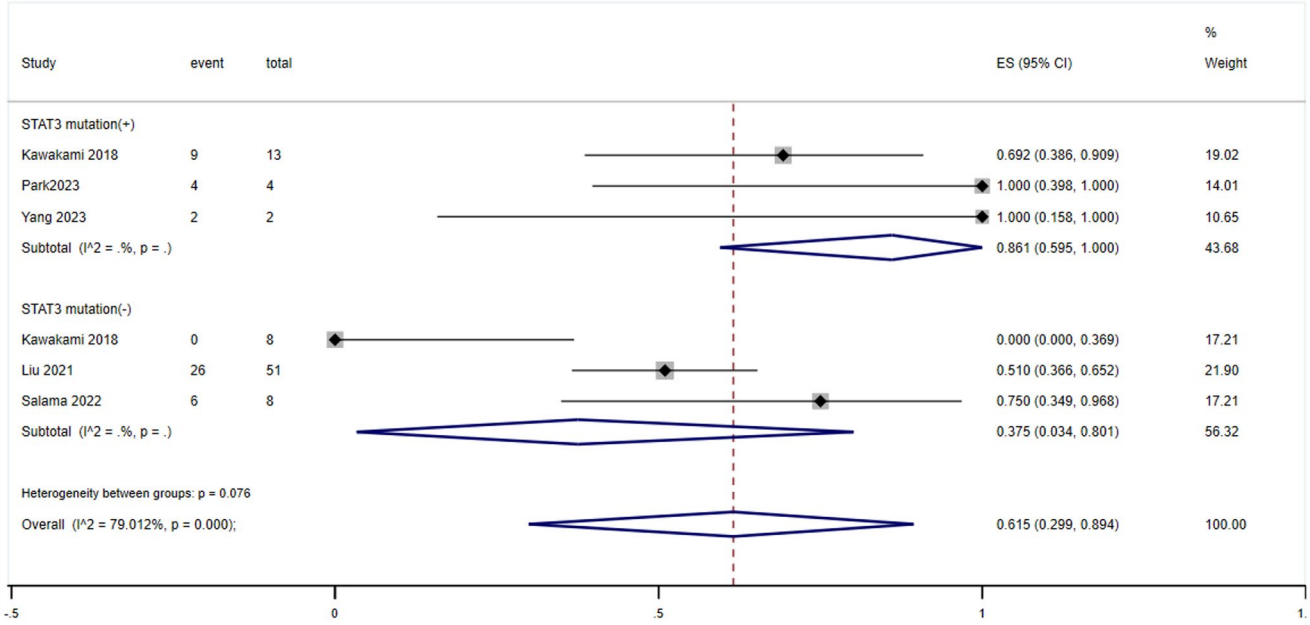

Fig. 9 Forest map of response rate of IST in different mutation groups

efficacy, their findings suggest that clonal hematopoiesis involving stem/progenitor cells may play a critical role in aPRCA pathophysiology. Such insights highlight the complexity of genetic factors in determining IST response and the need for further research to validate these associations.

Discussion

This systematic review with meta-analysis aimed to examine the effects of IST in aPRCA and identify the potential factors influencing treatment outcomes. The findings demonstrate a statistically significant overall response rate of 65.6%, with CsA emerging as the most effective treatment, followed by CYC and CS. These results align with previous study, which have made outstanding contributions to treating aPRCA with comprehensive and convincing outcom, provided critical insights into treating aPRCA and valuable guidance for designing prospective controlled studies to refine therapeutic strategies [51]. While the response rate of approximately 65% is widely recognized, a significant subset of patients continues to experience suboptimal outcomes in clinical settings. This result underscores the need for further research to identify determinants of IST efficacy and optimize individualized treatment approaches. Building upon the foundation of prior research, this study focused on analyzing influencing factors through subgroup analyses. Key findings include the impact of etiological differences, genetic mutations (e.g., STAT3), and treatment regimens (monotherapy vs. combination therapy and first-line therapy vs. second-line therapy) on IST outcomes. These insights contribute to a deeper understanding of the variables affecting IST efficacy and provide a basis for future research to improve patient outcomes in aPRCA.

The primary pathogenic mechanisms of aPRCA are thought to include direct damage to erythroid precursor cells by viruses or chemicals and antibody-mediated and/or cytotoxic lymphocyte-mediated suppression of erythropoiesis [5]. IST remains the treatment for primary aPRCA, LGLL-associated aPRCA, thymoma-associated aPRCA, and secondary aPRCA refractory to other therapies [1]. The primary treatment goal is to achieve normal hemoglobin concentrations without transfusions, with partial response defined as low but clinically acceptable hemoglobin levels without transfusion dependences [1]. Our analysis highlights the importance of etiological features in influencing the efficacy of IST, with response rates of 66.7%, 51.5%, and 69.0% in primary aPRCA, LGLL-associated aPRCA, and thymoma-associated aPRCA, respectively. These findings suggest that CsA demonstrates superior efficacy in primary and thymoma-associated aPRCA (77.5%), whereas CYC is the most effective agent for LGLL-associated aPRCA (73.3%). These insights provide valuable guidance for tailoring drug selection to individual patients in clinical practice. Notably, combination therapy, particularly CS and CsA, proved more effective (76.1%) than monotherapy and even higher than the combination of CS and CYC (66.4%). Wu et al. also reported that CsA combined with CS significantly improved the complete remission rate compared to CS alone ($P=0.009$) [29]. These findings suggest that combination therapies, initiated early in treatment, may yield better outcomes than monotherapies in managing aPRCA.

Our results showed no significant differences in the effectiveness of CS, CsA, and CYC as first-line therapy for aPRCA. All three agents exhibited comparable and substantial efficacy in this setting. However, their effectiveness as second-line treatments was notably diminished. For secondary aPRCA, treatment is typically centered on managing the underlying condition. In cases where the primary disease is untreatable or in primary aPRCA, IST remains the preferred treatment strategy [15, 43]. CsA, with or without CS, is commonly used as a first-line therapy in such instances. Our findings suggest that CS, CsA, and CYC have limited efficacy as second-line options, necessitating alternative approaches for patients who fail first-line treatments. Emerging evidence points to several promising second-line therapies, including tacrolimus, anti-thymocyte globulin (ATG), rituximab, and bone marrow transplantation. While these options have shown potential in refractory or recurrent aPRCA cases, most evidence stems from case reports or small studies, and these treatments are often associated with high costs and significant side effects [52]. Recently, novel agents such as sirolimus and daratumumab have been explored as potential treatments for refractory aPRCA. Preliminary evidence from small-scale studies and case reports suggests these drugs may offer improved efficacy [53]. However, robust clinical trials are needed to evaluate their effectiveness, safety, and feasibility on a larger scale. It is hoped that future research will focus on developing effective second-line therapies for aPRCA, emphasizing minimizing adverse effects and ensuring accessibility for broader patient populations.

Recent studies have highlighted significant advancements in understanding aPRCA, focusing on the roles of gene mutations, T-cell regulatory dysfunction, and clonal hematopoiesis [37]. The varied responses to IST among aPRCA patients underscore the heterogeneity of this condition [49]. Primary aPRCA is predominantly mediated by T-cells, although specific antibodies targeting erythroid progenitor cells have also been implicated in erythropoiesis suppression [54–56]. Despite the efficacy of IST, treatment failures and relapses remain common, partly due to limited insights into the disease's underlying mechanisms [57]. STAT3 is a latent transcription factor crucial for cytokine- and growth factor-mediated gene regulation. STAT3 plays a pivotal role in oncogenesis in its activated form, enhancing transformation and preventing apoptosis in various cancers [58]. Mutations in the SH2 domain, which mediates STAT3 dimerization and activation, result in a more hydrophobic protein surface, leading to increased phosphorylation and nuclear localization of STAT3. Functional studies have shown that mutations like Y640F and D661V significantly enhance STAT3's transcriptional activity, upregulating downstream genes such as IFNGR2, BCL2L1, and JAK2 [46]. Studies have identified STAT3 mutations in approximately 50% of LGLL patients, with common mutations including Y640F, D661Y, N647I, and E616V, all located in exons 20 and 21 encoding the SH2 domain. The mutations were restricted to CD8 + T-cell fractions in LGLL patients, indicating their role in clonal T-cell expansion [47]. The mutations were restricted to CD8 + T-cell fractions in LGLL patients, indicating their role in clonal T-cell expansion. For instance, LGLL patients with STAT3 mutations showed a higher incidence of anemia compared to those without mutations. STAT3 mutations were found in 25% of LGLL patients with aPRCA, compared to 4.8% in those without aPRCA ($P = 0.001$) [48]. Based on the above findings, it is believed that the STAT3 mutation may have an important role in the pathogenesis of aPRCA. STAT3 mutations are not limited to LGLL-associated aPRCA but have also been observed in primary and thymoma-associated aPRCA. Balasubramanian et al. reproted that 63 aPRCA patients, with 52% were primary, 22% LGLL-associated, and 15% thymoma-associated, and STAT3 mutations were prevalent across these subtypes [22, 23]. Additionally, comparison with other disorders, STAT3 mutations were absent in patients with aplastic anemia, paroxysmal nocturnal hemoglobinuria, or myelodysplastic syndromes, but were present in 43% of aPRCA patients, suggesting that STAT3 may serve as a specific biomarker for aPRCA [26]. Therefore, the frequent occurrence of STAT3 mutations in aPRCA and their absence in related hematological disorders may underscore their potential as specific biomarkers and pathogenic drivers of aPRCA. Aberrant STAT3 signaling likely contributes to the clonal expansion of CD8 + T cells and the suppression of erythroid progenitors, providing insights into the disease's molecular mechanisms and potential therapeutic targets.

Somatic mutations of STAT3 were frequently detected in $CD8^+$ T cells of aPRCA patients, implicating T-cell dysregulation as a central mechanism in the disease's pathogenesis. This phenomenon appears to be a common characteristic across primary aPRCA, LGLL-associated aPRCA, and thymoma-associated aPRCA, suggesting a shared pathogenic pathway [35]. STAT3-mutated $CD8^+$ T cells may thus be a clue to the unique pathophysiological background of aPRCA, irrespective of its etiology. In primary aPRCA, T-cell responses range from polyclonal to oligoclonal and ultimately monoclonal, reflecting the progressive imbalance of immune responses. It reflects the T-cell abnormalities observed in T-cell large granular lymphocytic leukemia (T-LGLL), representing these responses' most extreme monoclonal variant. STAT3 mutations provide a mechanistic basis for this progressive clonal skewing. Mutant STAT3 clonally derived CD8 + T cells are typically associated with TCR rearrangements, as identified by quantitative TCR Vβ chain sequencing in cytotoxic T lymphocytes (CTLs)

[46]. These clonal expansions of STAT3-mutant T cells are believed to mediate selective inhibition of erythroid progenitors, contributing to developing aPRCA. Thus, the frequent detection of STAT3-mutated CD8+T cells across aPRCA subtypes highlights the role of T-cell dysregulation in disease pathogenesis. These findings underscore the importance of targeting clonal T-cell populations in developing therapies for aPRCA.

STAT3 mutations have been implicated not only in the pathogenesis of aPRCA but also in treatment response. The two main mechanisms may target clonal changes in autoaggressive lymphocytes of red lineage progenitors and clonal hemopoiesis driven by somatic mutations in stem/progenitor cells during disease progression, which in turn leads to unresponsiveness to immunosuppression [46, 47]. Mutations in STAT3 have been identified across various subtypes of aPRCA [23, 26, 35]. Kawakami et al. reported that STAT3 mutated patients were less responsive to CsA than those with wildtype STAT3. These findings may indicate that clonal expansions of mutant lymphocytes may contribute to IST refractoriness. Liu et al. observed that patients with STAT3 mutations responded better to CTX than CsA (83.3% vs. 37.5%, $P=0.138$) [32]. Besides, Park et al. reported that all STAT3-mutated patients achieved complete or partial remission (100%, 13/13), compared to 66.6% (12/18) in the wildtype group ($P=0.028$) [38]. Therefore, these findings indicate that STAT3-positive patients may exhibit increased sensitivity to IST, particularly in LGLL-associated aPRCA. However, Kawakami et al. found no significant differences in the overall response rate to IST between patients with and without STAT3 mutations [35]. Our study also found that the response rate to IST was significantly higher in STAT3-mutation-positive patients (86.1%) compared to those without mutations (37.5%). This result suggests that STAT3 mutation status could serve as a predictive marker for treatment outcomes and guide the choice of therapeutic regimens. However, the lack of clarity regarding the pathological mechanisms linking STAT3 mutations to IST responsiveness contributes to the conflicting outcomes of current studies. Additionally, our findings are derived from a limited sample size, which reduces the robustness of conclusions and highlights the need for further research. Despite these limitations, our results provide valuable insights for future investigations into the role of STAT3 mutations in the development, drug efficacy, and prognosis of aPRCA.

This study provides a comprehensive summary of the effectiveness of common immunosuppressive drugs in treating aPRCA and explores factors influencing their efficacy, a topic that has been underexplored in the literature. However, there are several limitations to this systematic review and meta-analysis. The included studies are predominantly retrospective, making them prone to selection bias and limiting the ability to establish causation. Significant heterogeneity exists among the included case series, driven by differences in study designs, patient populations, and reporting standards. Many studies included small cohorts, reducing the statistical power of subgroup analyses and limiting generalizability. The use of differing treatment regimens and protocols across centers further complicates the interpretation and synthesis of results. Despite these limitations, this meta-analysis addresses a critical gap by providing evidence-based insights into treating a rare condition like aPRCA, where robust data are often lacking. The findings underscore the need for standardized treatment protocols and larger, prospective studies to confirm these results and refine therapeutic strategies [59]. Future research should focus on overcoming the current limitations by employing prospective study designs, ensuring consistent treatment protocols, and including larger patient populations to enhance the validity and applicability of findings.

Author contributions JianPing Hao and GuangSheng He conceived and designed this study. Yusup Muyassar, YuTing Qin, Niluopaer Tuerxun were responsible for the collection, extraction, and analysis of the data. Yusup Muyassar, JianPing Haowas responsible for writing the paper. YuTing Qin, Niluopaer Tuerxun performed the quality evaluation and completed data analysis. Yusup Muyassar polished the English language. All authors and participants reviewed the paper and reached an agreement to approve the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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