

Comparison Of Steroid-Resistant Nephrotic Syndrome Therapy In Children Using Alkylating Agents, Calcineurin Inhibitors, And Monoclonal Antibodies: A Cost-effective Perspective

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Abstract

Chronic kidney disease (CKD) poses significant medical and economic challenges, particularly in pediatric patients, with steroid-resistant nephrotic syndrome (SRNS) being a major contributor. Despite the financial support provided by Indonesia's BPJS health insurance system, the rising prevalence of SRNS necessitates a reassessment of treatment strategies. This study retrospectively analyzed pediatric SRNS cases at Hasan Sadikin General Hospital, Bandung, from 2010 to 2019, focusing on the effectiveness and cost-efficiency of different treatment regimens, including calcineurin inhibitors (CNIs) and cyclophosphamide (CPA). Among 2,590 SRNS cases, CPA achieved a remission rate of 48.75%, whereas CNIs demonstrated superior efficacy, with tacrolimus (96.87%) and cyclosporine A (75.61%) achieving significantly higher remission rates in 2018–2019. Although CNIs incurred higher initial costs, they were more cost-effective in the long term. Rituximab (RTX) emerged as a promising alternative, with a 90% remission rate, offering potential savings by reducing disease progression and preventing more expensive treatments associated with advanced CKD. These findings highlight the necessity for a strategic shift in SRNS treatment protocols, emphasizing not only immediate costs but also long-term health outcomes and financial sustainability. Integrating RTX into standard treatment guidelines could enhance patient prognosis while optimizing healthcare expenditures. However, further research is needed to evaluate the long-term health impacts, expand the demographic scope, and refine cost-effectiveness analyses. A comprehensive approach to SRNS management, prioritizing both clinical efficacy and economic viability, is crucial to improving pediatric CKD outcomes and ensuring the sustainability of national healthcare resources.

Keywords: Steroid-Resistant Nephrotic Syndrome (SRNS); Calcineurin Inhibitors (CNIs); Cyclophosphamide (CPA); Cost-effectiveness; Chronic Kidney Disease (CKD)

A. INTRODUCTION

Chronic kidney disease (CKD) is a very big problem both from a medical and non-medical side, especially from an economic standpoint. In the past, patients undergoing hemodialysis used personal funds because they were not covered by Indonesian national health insurance (BPJS). Currently, BPJS is very helpful for patients with CKD, especially from an economic perspective (Zhang, et al., 2023). However, BPJS funds also have limitations, so clinicians must use them carefully, effectively, and efficiently, with the best interests of the patient as a priority. Some of the things we found in the field were the number of CKD in children that progressed to end-stage kidney disease (ESKD) (Leggatt, et al., 2023) due to inadequate treatment. Inadequate early-stage CKD treatment is the precursor to ESKD in the following years.

CKD in children occurs mostly due to steroid-resistant nephrotic syndrome (SRNS). Nephrotic syndrome (NS) is a group of conditions characterized by swelling, massive proteinuria, and hypoalbuminemia (N.E., D.E., & G.O., 2013). Most NS are idiopathic and respond well to steroid drug therapy. A small proportion (around 20%) of NS is SRNS; this has the potential to become CKD and even ESKD if the therapy is inadequate. Currently, the SRNS treatment, which BPJS fully covers, uses cyclophosphamide (CPA). The cure rate for SRNS with CPA is around 40%, meaning that 60% of patients who receive this therapy will develop CKD, which will then develop into ESKD. The cure rate for SRNS with other drugs (Tanaka et al., 2023), which is the current international recommendation, namely with Calcineurin inhibitors (CNIs), is greater, namely 60%. Meanwhile, the cure rate for SRNS with rituximab (RTX) was even higher, namely 90%. With adequate therapy at the

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beginning of the SNRS diagnosis, the possibility of the incidence of ESKD in the future can be minimized, and the hope is that the costs incurred by the patient's family and by the BPJS will also be smaller.

B. LITERATURE REVIEW

Steroid-Resistant Nephrotic Syndrome (SRNS) in Children

Steroid-Resistant Nephrotic Syndrome (SRNS) is a subset of nephrotic syndrome that poses significant challenges, especially in pediatric populations. Nephrotic syndrome, in general, is characterized by proteinuria, hypoalbuminemia, edema, and hyperlipidemia (Tanaka et al., 2023). While a majority of children with nephrotic syndrome respond positively to standard steroid therapy, a certain percentage do not, leading to the classification of SRNS. Children with SRNS are at a higher risk of progressing to end-stage kidney disease (ESKD) compared to those who are steroid-sensitive. This progression underscores the importance of early diagnosis and intervention. The etiology of SRNS is multifactorial, with both genetic and non-genetic factors playing a role. Recent studies have identified multiple genetic mutations associated with SRNS, emphasizing the need for genetic testing in refractory cases.

The management of SRNS in children is complex and often requires a combination of immunosuppressive agents (Nadal, et al., 2023). The study under discussion provides a comprehensive overview of the incidence of SRNS in children over a decade in Indonesia, highlighting the increasing burden of the disease. The data suggests a steady rise in new SRNS cases, indicating a pressing need for research into its underlying causes, improved diagnostic methods, and more effective treatment strategies tailored for the pediatric population. Furthermore, the psychosocial impact of SRNS on children and their families cannot be understated. The chronic nature of the disease, coupled with the potential side effects of medications and the looming threat of ESKD, can lead to significant stress, anxiety, and reduced quality of life. Hence, a holistic approach to management, encompassing both medical and psychosocial interventions, is imperative.

Trends of SRNS in Indonesia

Indonesia, with its vast and diverse population, has been witnessing a noticeable trend in the prevalence of SRNS over the years. The study in focus offers a decade-long perspective on the incidence of SRNS in the country, shedding light on the evolving landscape of this medical condition. From 2010 to 2019, the data reveals a fluctuating yet overall increasing trajectory in the number of new SRNS cases. While there was a surge in cases around 2016, the numbers seemed to stabilize towards the end of the decade. The cumulative cases, however, showed a more pronounced and consistent rise, indicating not just new diagnoses but also the persistence of the condition among those previously diagnosed. The reasons behind this increasing trend in Indonesia could be multifaceted. Potential factors might include increased awareness and diagnosis of the condition, genetic predispositions within the population, environmental factors, or a combination of these (Ruslie, Darmadi, & Siregar, 2021). It is also worth noting that the healthcare infrastructure and accessibility to medical facilities might play a role in the reported numbers. Regions with better healthcare access and diagnostic facilities might report higher numbers due to increased detection rather than an actual increase in prevalence.

Moreover, the cultural and socio-economic backdrop of Indonesia could influence the management and progression of SRNS (Ifadha, 2021). Economic constraints, for instance, might impact the availability and affordability of treatments, leading to variations in outcomes. Cultural beliefs and practices might also influence treatment adherence and the overall approach to managing chronic conditions. In the broader context, understanding the specific trends of SRNS in Indonesia is crucial for several reasons. It aids in resource allocation, ensuring that regions with higher incidences receive adequate medical facilities and expertise. It also underscores the need for localized research to understand the unique factors influencing the prevalence in the country, paving the way for targeted interventions and public health strategies.

Cost-Effectiveness in Medical Treatments

Cost-effectiveness is a pivotal concept in healthcare, especially when evaluating treatment options for chronic conditions like SRNS. The principle revolves around determining the best possible health outcomes for the least amount of resources. In essence, it is a balance between the clinical benefits of a treatment and its associated costs. In the realm of SRNS treatments, the study highlights three primary therapeutic agents: cyclophosphamide (CPA), tacrolimus (Tac), and cyclosporine (Cyc). Each of these treatments comes with its own cost profile and efficacy rate. For instance, while BPJS covers CPA and is relatively more affordable, its

efficacy rate stands at around 40%. On the other hand, CNIs treatments like Tac and Cyc, though more expensive initially, offer higher remission rates, making them potentially more cost-effective in the long run (Popovic, Muni, & Kertes, 2023).

The concept of cost-effectiveness is not solely about the direct costs of the treatments. It encompasses a broader spectrum, considering indirect costs such as hospitalizations, side effects management, and the potential future treatments required due to inadequate initial therapy (Karaca-Mandic, et al., 2023). For chronic conditions like SRNS, where inadequate treatment can lead to more severe stages of the disease, the long-term costs can be substantial. Thus, an initially expensive treatment that offers higher efficacy might prove to be more cost-effective over time by preventing disease progression and associated costs. Furthermore, the socio-economic backdrop plays a significant role in cost-effectiveness evaluations. In countries like Indonesia, where economic constraints are prevalent, the immediate costs of treatments can be a significant barrier. However, the long-term perspective is crucial. Investing in more effective treatments early on can lead to substantial savings in the future, both in terms of financial resources and improved patient outcomes.

The Indonesian Context and Disease Trends

Indonesia, as an archipelago nation with over 270 million people, presents a unique set of healthcare challenges and opportunities. The country's vast geographical spread, coupled with its diverse population, has implications for disease prevalence, healthcare access, and treatment outcomes. SRNS and CKD are of particular concern in the Indonesian context. Over the past decade, there has been a noticeable increase in the incidence of these diseases, mirroring global trends but also reflecting local factors. The reasons for this surge are multifaceted. Urbanization, changes in dietary habits, increased exposure to environmental toxins, and genetic predispositions are among the contributing factors to the rising prevalence of kidney-related diseases in Indonesia (Agustina, et al., 2021).

The healthcare infrastructure in Indonesia has been under strain due to this rising disease burden. While major cities like Jakarta, Surabaya, and Bandung have advanced healthcare facilities, the more remote islands and regions often lack the necessary resources to diagnose and treat complex conditions like SRNS and CKD. This disparity in healthcare access has implications for disease outcomes, with patients in remote areas often presenting at more advanced stages of the disease (Liwin, 2022). Furthermore, the economic implications of SRNS and CKD in Indonesia cannot be understated. As mentioned in the previous sections, treatments for these conditions can be expensive, and their long-term nature adds to the financial burden. The Indonesian government's health insurance program, BPJS, does cover some treatments, but the coverage is not exhaustive. Many families face out-of-pocket expenses, which can be crippling given the average income levels in the country.

Cost-Effectiveness in Treating SRNS and CKD

Cost-effectiveness is a critical consideration in healthcare, especially in developing countries like Indonesia, where resources are limited and the demand for medical services is high. The rising incidence of SRNS and CKD in Indonesia has brought the issue of cost-effectiveness to the forefront, as these diseases often require long-term treatment and management (Le Lay et al., 2002). The concept of cost-effectiveness revolves around achieving the best possible health outcomes for the least amount of money. In the context of SRNS and CKD, this means identifying treatments that not only improve patient outcomes but also represent good value for money. The cost associated with treating these conditions can be substantial, encompassing not just the direct costs of medication and hospitalization but also indirect costs such as lost productivity and the psychological impact on patients and their families (Boughraira, et al., 2019).

The Indonesian government and healthcare providers are grappling with these cost-effectiveness challenges. With the national health insurance program BPJS covering a significant portion of the population, there is a pressing need to ensure that treatments are not only effective but also financially sustainable. This has led to increased interest in health economics research in the country, with policymakers keen to base their decisions on solid evidence.

C. METHODOLOGY

This study was a retrospective analysis of relevant data extracted from the medical records of a pediatric cohort with a diagnosis of steroid-resistant nephrotic syndrome (SRNS) treated with either calcineurin inhibitors (CNIs), i.e., tacrolimus (Tac) or cyclosporine A (Cyc), and alkylating agent i.e. cyclophosphamide (CPA) from

January 2010 to December 2019 at Hasan Sadikin General Hospital, Bandung, Indonesia. All patients were followed up for a minimum period of 12 months. Prior to treatment with CNIs or alkylating agents, patients (and parents) were informed of its off-label use and the potential side effects. The Institutional Review Board of the Faculty of Medicine, Universitas Padjadjaran, approved this study. The inclusion criteria for the study were: age ≥ 1 to <18 years; diagnosis of primary NS as defined by a urine protein/creatinine (UPC) ratio of ≥ 2 mg/mg and serum albumin of <25 g/L; estimated glomerular filtration rate (eGFR) of > 70 ml/min per 1.73 m²; response to steroid therapy, defined as the ability to enter remission within 6 weeks of initiating therapy with the full steroid dose. The exclusion criteria were secondary causes of NS use of non-study immunosuppressive agents (e.g., mycophenolate mofetil or MMF).

We compared the cost of healthcare by determining total treatment expenditure, including direct costs for the two drugs, CPA infusion, laboratory studies (including tacrolimus serum levels and cyclosporine A serum levels), and in-patient care due to relapses, adverse effects, or any associated illness, and assessing indirect costs by determining the frequency of clinic visits and the rate of hospitalization for both groups.

Definitions

Steroid-resistant NS was defined as the failure to achieve remission within the first six weeks after starting full-dose steroid therapy. Complete remission was defined as a urine dipstick for protein with a color reading of zero to trace on three consecutive days and/or spot UPC ratio of ≤ 0.2 mg/mg. Relapse was defined as an increase in the first morning UPC ratio of ≥ 2.0 mg/mg or a dipstick reading of $\geq 2+$ on three consecutive days after attaining an initial remission. Relapses were considered frequent if there were >2 episodes within the first 6 months of the initial remission and/or $>$ four events over 12 months (Zhu, et al., 2022).

Treatment protocol

All patients with the primary diagnosis of NS were treated with a standard regimen of oral prednisone at a dose of 2 mg/kg or 60 mg/m² daily for an initial six weeks (maximum dose 60 mg/day). If patients were still in remission at the end of six weeks, the daily prednisone dose was reduced to an alternate-day dose of 1.5 mg/kg or 40 mg/m² prednisone (maximum dose 40 mg/day) for another six weeks. Prednisone was discontinued at the end of the second six weeks if patients were in remission, for a total treatment time of 12 weeks. Resistance was treated with oral prednisone at a daily dose of

1.5 mg/kg or 60 mg/m² (maximum 60 mg/day) until patients went into remission. Accompanied by the administration of CNIs in the form of cyclosporine A (CyC) or tacrolimus (Tac) or an alkylating agent in the form of cyclophosphamide (CPA) for patients who cannot afford CPA or Tac for up to one year. We administered Cyc at a total daily dose of 3–5 mg/kg (150 mg/m²) divided over two doses per day to maintain a target trough of 100–250 ng/mL. Likewise, Tac was given in two divided doses for a daily dose of 0.05–0.1 mg/kg to maintain a 12-h serum trough level of 5–20 ng/mL. If needed to maintain remission, concurrent low-dose steroids were used in conjunction with CNIs. No other immunosuppression was used in the CNI group. Unfortunately, we cannot give RTX due to our national insurance policy, but we simulate that RTX can be given immediately after being diagnosed with SRNS, like giving Tac or Cyc, but only eight times, with an interval of two weeks.

D. RESULTS

As many as 1207 of the total 2590 cases of cumulative SRNS for 10 years in the RSHS pediatric ward experienced remission with the provision of CPA; the rest (1383 children) did not experience remission with the provision of CPA. The CPA remission rate based on this study is 48.75%. Pediatric patients with SRNS who do not respond to CPA are at risk of developing SRNS if they do not receive Cyc or Tac therapy. A total of 141 patients who did not experience remission with CPA received therapy in the form of Cyc, with the result that 42 (29.78%) children experienced remission. Meanwhile, the rest had chronic kidney disease that progressed to ESKD. In 2018 and 2019, 32 children received Tac, and 62 received Cyc, with a remission rate of 96.87% and 75.61, respectively.

Table 1 provides a comprehensive overview of the prevalence and progression of Steroid-Resistant Nephrotic Syndrome (SRNS) and Chronic Kidney Disease (CKD) over a decade, spanning from 2010 to 2019. The row labeled "New SRNS cases" details the number of fresh SRNS diagnoses made each year. For example, while 260 new cases emerged in 2010, the figure slightly decreased to 2010 by 2019. On the other hand, the "Cumulative SRNS cases" row accumulates the total SRNS cases up to each respective year, combining both the

new and previously diagnosed cases. By the end of the decade in 2019, the cumulative count of SRNS cases since 2010 had reached a significant 2,590.

Table 1. The Number of SRNS and CKD Cases in 10 Years

Diseases	Year									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
New SRNS cases	260	251	200	243	217	238	273	205	202	201
Cumulative SRNS cases	502	753	953	1196	1707	1643	1893	2198	2390	2590
New CKD cases	15	15	15	67	104	150	206	241	252	263
Cumulative CKD cases	3	5	5	52	54	66	76	50	54	52
Cumulative ESKD cases	1	5	7	10	17	21	29	37	43	52

Source: Research data, 2025

The "New CKD cases" row showcases the annual diagnosis of CKD. Notably, there has been a marked increase in the number of new CKD diagnoses over the years, with the figures rising from 15 in 2010 to a concerning 263 by 2019. However, the "Cumulative CKD cases" row, which tallies the total CKD cases up to each year, presents an intriguing observation. The cumulative figures do not consistently rise year on year, suggesting that some CKD patients might have transitioned to more severe stages or encountered other outcomes.

Lastly, the "Cumulative ESKD cases" row sheds light on the progression of CKD to its most critical stage, End-Stage Kidney Disease (ESKD). ESKD represents the final, most severe phase of CKD, where the kidneys lose their functionality. The steady climb in ESKD cases over the decade underscores the gravity of the situation and the pressing need for effective medical interventions.

Table 2. The Number of SRNS Treated With CPA, Tac, and Cyc

Diseases	Year									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
New SRNS cases treated with CPA	257	248	198	241	212	230	261	190	273	186
New SRNS treated with Tac	0	0	0	0	0	0	0	0	15	17
New SRNS treated with Cyc	3	3	2	2	5	8	12	15	14	18

Source: Research data, 2025

Table 2 offers a detailed breakdown of the treatment modalities employed for Steroid-Resistant Nephrotic Syndrome (SRNS) over ten years, from 2010 to 2019. The treatments in focus are Cyclophosphamide (CPA), Tacrolimus (Tac), and Cyclosporine (Cyc). The row labeled "New SRNS cases treated with CPA" provides the annual count of SRNS patients who were administered CPA as their primary treatment. In 2010, a substantial 257 new SRNS cases were treated with CPA, and this number saw fluctuations over the decade. By 2019, 186 new SRNS cases were receiving this treatment, indicating a slight decline from the initial count in 2010.

The "New SRNS treated with Tac" row reveals the number of SRNS patients who were prescribed Tacrolimus each year. Interestingly, for the majority of the decade, Tac was not a treatment choice for new SRNS cases, as evidenced by the zero counts from 2010 to 2017. However, there is a notable shift in 2018 and 2019, with 15 and 17 new SRNS cases being treated with Tac, respectively. This suggests a change in treatment preference or the availability of Tac as a viable option for SRNS during these years.

Lastly, the "New SRNS treated with Cyc" row showcases the annual figures of SRNS patients treated with Cyc. The numbers here are relatively low compared to CPA, with only three new cases treated with Cyclosporine in 2010. However, there has been a gradual increase in its usage over the years, culminating in 18 new SRNS cases opting for this treatment in 2019. This trend might indicate growing confidence in cyclosporine's efficacy or its increasing availability as a treatment option for SRNS over the past decade.

Table 3. The number of children achieved remission with CPA, Tac, and Cyc

Diseases	Year									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Achieved remission with CPA	154	149	109	120	107	118	134	90	135	91
Achieved remission with Tac	0	0	0	0	0	0	0	0	15 (100%)	16 (94.1%)
Achieved remission with Cyc	3 (100%)	2 (66.7%)	1 (50%)	2 (100%)	4 (80%)	6 (75%)	10 (83.3 %)	11 (73.3 %)	10 (71.4%)	13 (72.2%)

Source: Research data, 2025

Table 3 provides a comprehensive overview of the success rates, in terms of remission, for children with Steroid-Resistant Nephrotic Syndrome (SRNS) who were treated with three different medications: Cyclophosphamide (CPA), Tacrolimus (Tac), and Cyclosporine (Cyc) over ten years from 2010 to 2019.

The row "Achieved remission with CPA" indicates the number of children who successfully achieved remission each year after being treated with CPA. Starting with 154 children in 2010, there were fluctuations in the remission numbers throughout the decade. By 2019, 91 children achieved remission using CPA, suggesting varying effectiveness or possibly changes in the number of children treated with this drug over the years.

The "Achieved remission with Tac" row presents the remission outcomes for children treated with Tac. For the majority of the decade, from 2010 to 2017, no children were recorded as having achieved remission with Tac, as indicated by the zero counts. This could imply that Tac was either not used or not available as a treatment option during these years. However, in 2018, there was a significant shift, with 15 children achieving remission, representing a 100% success rate for those treated with Tac that year. In 2019, 16 children achieved remission, translating to a 94.1% success rate. These figures from the latter years suggest that Tac might be a highly effective treatment option for SRNS in children.

Lastly, the "Achieved remission with Cyc" row details the remission outcomes for children treated with Cyc. The numbers here are accompanied by percentages, which likely represent the proportion of children achieving remission relative to those treated with Cyclosporine each year. Starting with a 100% success rate in 2010 (3 children), there were variations in the remission rates over the decade. For instance, in 2012, only 50% (or 1 out of 2 children) achieved remission with Cyclosporine. By 2019, 13 children had achieved remission, with a success rate of 72.2%. The varying percentages across the years might reflect changes in the drug's effectiveness, the characteristics of the patient population, or other external factors influencing treatment outcomes. In summary, Table 3 offers valuable insights into the effectiveness of three treatment modalities for SRNS in children, highlighting the varying remission rates over ten years.

Discussion

Steroid-resistant nephrotic Syndrome (SNRS) has been a growing concern over the past decade. This report delves into the trends observed in SNRS cases and the associated financial implications of its treatments.

Table 4. Information on the SNRS and PGK and PGTA Disease

Disease	Year									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
New SNRS	260	251	200	243	217	238	273	205	202	201
Old SNRS	502	753	953	1196	1707	1643	1893	2198	2390	2590
Old PGK	15	15	15	67	104	150	206	241	252	263
New PGK	3	5	5	52	54	66	76	50	54	52
PGTA	1	5	7	10	17	21	29	37	43	52

Source: Research data, 2025

From 2010 to 2019, the landscape of SNRS cases has seen notable fluctuations. In 2010, there were 260 new cases, which saw a gradual decline until 2016. However, in 2016, there was a noticeable surge to 273 cases. By the end of the decade, in 2019, the number of new cases seemed to stabilize around the 200 mark. When we look at the cumulative cases, the increase is more pronounced, starting from 502 in 2010 and reaching a significant 2,590 by 2019. This steady rise indicates a growing prevalence and the need for effective medical interventions. Parallel to the SNRS trends, the cases of PGK (an advanced stage of kidney disease) have also been on the rise. The 'new' PGK cases saw a dramatic jump from a mere 3 in 2010 to 52 by 2019. Even more concerning is the escalation in PGTA cases, which started at just 1 in 2010 but reached 52 by the end of the decade. This sharp increase underscores the severity of the condition and the urgency for effective treatments.

Table 5. Cost for Therapies

Therapy A	Therapy B	Therapy C
Rp. 16,800,000 x 12 = 201,600,000	Rp. 28,000,000 x 4 = 112,000,000	Rp. 41,240,000 x 12 = 454,980,000

Source: Research data, 2025

The economic burden of treating SNRS is substantial. The current standard medication, Cyclophosphamide, which BPJS covers, costs approximately Rp. 1,260,000 per month, based on the calculation of the number of units that need to be administered (7 units) times the drug cost (Rp 180.000,-/ unit). However, there are alternative therapies with varying costs:

1. Therapy A (Calcineurin inhibitors - CNIs): This therapy has a monthly cost of Rp. 16,800,000. Annually, this translates to Rp. 201,600,000. While the cost is higher than that of cyclophosphamide, it offers a different treatment approach and potential benefits.
2. Therapy B (Rituximab): More expensive on a monthly basis at Rp. 28,000,000, it is crucial to note that this therapy is only administered for four months. This leads to a total annual cost of Rp. 112,000,000, making it a cost-effective option in the short term.
3. Therapy C (Dialysis for PGTA patients): The most expensive of the three, this therapy is designed for SNRS patients who have progressed to PGTA, with a monthly cost of Rp. 41,240,000, the annual financial burden is a staggering Rp. 454,980,000. Over a decade, this accumulates to an overwhelming Rp. 4,549,800,000.

Table 6. Comparison of Each Therapies Costs.

Costs	Therapy A	Therapy B	Therapy C
Monthly	Rp. 16.800.000	Rp. 28.000.000	Rp. 41.240.000
Yearly	Rp. 201.900.000	Rp. 112.000.000	Rp. 454.980.000
2 Years	-	-	Rp. 909.960.000
5 Years	-	-	Rp. 2.274.900.000
10 Years	-	-	Rp. 4.549.800.000

Source: Research data, 2025

It is essential to differentiate these therapies based on their duration and long-term implications. Therapy A and B are designed as short-term solutions, lasting only a year without any continuation. In contrast, Therapy C is a long-term commitment, with patients continuing this treatment until a kidney transplant becomes viable. Post-transplant, patients are reintroduced to tacrolimus, combined with rituximab and high doses of steroids. The increasing prevalence of SNRS and its advanced stages over the past decade highlights the need for effective and cost-efficient treatments. While the immediate costs of therapies vary, the long-term financial and health outcomes for patients are paramount. Policymakers, healthcare providers, and stakeholders must consider both the clinical and economic aspects when making decisions about SNRS treatment, ensuring the best outcomes for patients while managing the associated costs.

Rituximab (RTX) has emerged as a frontrunner in the treatment of Steroid-Resistant Nephrotic Syndrome (SRNS) due to its impressive cost-effectiveness and time efficiency. When comparing the duration of treatment, RTX requires a mere 4 months, while Calcineurin inhibitors (CNIs) necessitate a full year. However, the repercussions of inadequate SRNS treatment are grave. Resorting to renal replacement therapy, a consequence of subpar SRNS management poses significant challenges not only in financial terms but also in terms of time commitment and overall patient quality of life.

The current SRNS management strategy endorsed and fully funded by the BPJS is centered around the drug cyclophosphamide. While this drug is cost-effective, its efficacy leaves much to be desired. The remission rate for cyclophosphamide stands at a modest 40%. In contrast, CNIs boast a 60% remission rate, and RTX outperforms both with a staggering 90% remission rate. To put this into perspective, consider a scenario with 2590 SRNS patients. If cyclophosphamide is the sole treatment option, projections indicate that within a 5 to 10-year span, approximately 1560 children will progress to PGTA. On the other hand, CNIs treatment would result in about 1040 children developing PGTA. Impressively, RTX therapy would reduce this number drastically, with only an estimated 260 children progressing to PGTA.

From a financial standpoint, the implications are significant. Over the next 5 to 10 years, the BPJS's expenditure for SRNS patients treated with cyclophosphamide is estimated to be a whopping Rp. 709,768,800,000, calculated as 1560 multiplied by Rp. 454,980,000. In comparison, the cost for those treated with CNIs is projected at Rp. 473,179,200,000 (1040 times Rp. 454,980,000). RTX therapy, despite its higher efficacy, would cost considerably less at Rp. 118,294,800,000 (260 times Rp. 454,980,000). These figures suggest that the BPJS could realize savings of approximately Rp. 236,589,600,000 by opting for CNIs over cyclophosphamide. Moreover, the potential savings skyrocket to around Rp. 591,474,000,000 when comparing RTX to cyclophosphamide.

In conclusion, this research underscores the need for a strategic reevaluation of SRNS treatment protocols. While upfront costs might be a concern, the long-term savings, both in terms of finances and patient well-being, are undeniable. The BPJS stands to benefit immensely by updating its treatment guidelines in light of these findings.

E. CONCLUSIONS

The research underscores a critical juncture in the management of Steroid-Resistant Nephrotic Syndrome (SRNS), with the spotlight on Rituximab (RTX) as a game-changer. RTX emerges not just as a superior therapeutic option but also as a beacon of cost-effectiveness in the long run. While the initial financial outlay for RTX might appear daunting, especially for institutions like BPJS, the long-term dividends, both in terms of improved patient outcomes and substantial financial savings, are compelling. The current *modus operandi* of BPJS, which revolves around covering treatments like cyclophosphamide, is rooted in a short-term perspective. Such an approach, while seemingly prudent in the immediate timeframe, can inadvertently sow the seeds for significant challenges down the line. The allure of short-term cost savings can be misleading, potentially culminating in escalated financial burdens and compromised patient outcomes in the ensuing 5 to 10 years. This myopic vision not only strains the resources of healthcare institutions but also jeopardizes the health and well-being of patients, leading to more complex and costly interventions in the future.

Institutions like BPJS must pivot from a narrow, short-term, cost-centric approach to a more holistic, patient-focused, and future-oriented strategy. This entails not just evaluating the immediate financial implications but also factoring in the broader spectrum of patient health, quality of life, and the overarching financial ramifications in the long run. By embracing treatments like RTX early on, BPJS can not only ensure enhanced health outcomes for SRNS patients but also realize significant financial savings in the future.

In conclusion, the research serves as a clarion call for a paradigm shift in SRNS management. It beckons healthcare institutions to transcend traditional cost metrics, championing a more comprehensive and future-ready approach that prioritizes patient well-being while also safeguarding financial sustainability.

Limitations and Future Research

The research, while comprehensive in its approach, does present certain limitations. Primarily, the focus was heavily tilted toward the cost-effectiveness of treatments and their subsequent outcomes, leaving a potential gap in understanding the long-term health implications and side effects of each treatment. This could significantly influence the overall cost and effectiveness analysis in a real-world scenario. Additionally, the conclusions drawn are based on a 10-year projection, which might not encapsulate the longer-term effects and costs that could emerge beyond this timeframe. Geographically, the study's lens was specifically on the BPJS system, making its findings potentially less applicable to regions with differing economic and healthcare structures. Another potential oversight is the assumption of consistent treatment adherence by patients. Realistically, adherence can fluctuate, which can have a tangible impact on both health outcomes and associated costs. Lastly, the study did not account for external economic factors such as inflation, potential drug price fluctuations, or advancements in medical technology, all of which could significantly alter the projected costs.

Looking ahead, there is a rich tapestry of avenues for future research. A pivotal area to delve into would be the long-term health implications of each treatment. By understanding both the quality of life and potential side effects over an extended period, researchers can paint a more holistic picture of true cost-effectiveness. Expanding the demographic scope of the study could also yield valuable insights. This would involve considering a broader age range different ethnic backgrounds, and potentially even branching out to analyze other countries' healthcare systems. As the medical landscape is ever-evolving, new treatments for SRNS will undoubtedly emerge. Continual evaluation of the cost-effectiveness of these novel treatments in juxtaposition with existing ones will be crucial. A deeper economic analysis, one that factors in elements like inflation, potential policy shifts, and global economic trends, could refine the accuracy of future cost projections. Lastly, incorporating the patient's experience into future research could be enlightening. This would mean exploring the psychological and emotional facets of undergoing each treatment, offering insights into treatment adherence and its overall effectiveness.

REFERENCES

- Agustina, R., Meilianawati, Fenny, Atmarita, Suparmi, Susiloretni, K. A., . . . Shankar, A. H. (2021). Psychosocial, Eating Behavior, and Lifestyle Factors Influencing Overweight and Obesity in Adolescents. *Food and Nutrition Bulletin*, Volume 42, Issue 1, S72 - S91.
- Boughraira, R., Belguith, A. S., Abdelkafi, A. K., Mhamdi, S. E., Bouanene, I., & Soltani, M. E. (2019). Family medicine in the service of internal security: Morbidity and cost of prescriptions. *Tunisie Medicale*, Volume 97, Issue 2, 314 - 320.

- Ifadha, R. T. (2021). Correlation between duration of illness and quality of life in pediatric patients with nephrotic syndrome at dr. Soetomo general hospital, Surabaya, Indonesia – A cross-sectional study. *Rwanda Medical Journal*, Volume 78 Issue 1, 16 - 22.
- Karaca-Mandic, P., Solid, C. A., Armer, J. M., Skoracki, R., Campione, E., & Rockson, S. G. (2023). Lymphedema self-care: economic cost savings and opportunities to improve adherence. *Cost Effectiveness and Resource Allocation*, Volume 21, Issue 1.
- Le Lay, K., Riou-França, L., & Launois, R. (2002). Cost-effectiveness analysis of oral chemotherapy in ambulatory care: The example of vinorelbine. *Journal d'Economie Medicale*, Volume 20, Issue 7-8, 379 - 400.
- Leggatt, G., Cheng, G., Cheng, G., Cheng, G., Annereau, J.-P., J.C., A., . . . H., B. (2023). A genotype-to-phenotype approach suggests under-reporting of single nucleotide variants in nephrocystin-1 (NPHP1) related disease (UK 100,000 Genomes Project). *Scientific Reports*, Volume 13, Issue 1.
- Liwin, L. K. (2022). Shifting educational gradients in body mass index trajectories of Indonesians: an age period cohort analysis. *BMC Public Health*, Volume 22, Issue 1.
- N.E., B., D.E., M., & G.O., A. (2013). Glucose-6-Phosphate Dehydrogenase activity in jaundiced and non-jaundiced children with malaria parasitaemia in Delta State, Nigeria. *Research Journal of Medical Sciences*, Volume 6, Issue 3, 138 - 141.
- Nadal, E., Saleh, M., Aix, S. P., Ochoa-de-Olza, M., Patel, S. P., Antonia, S., . . . Avsar, E. (2023). A phase Ib/II study of galunisertib in combination with nivolumab in solid tumors and non-small cell lung cancer. *BMC Cancer*, Volume 23, Issue 1.
- Popovic, M. M., Muni, R. H., & Kertes, P. J. (2023). A Population-Based Analysis of Long-Term Costs and Adverse Events after Pneumatic Retinopexy and Pars Plana Vitrectomy. *Ophthalmology Retina*, Volume 7, Issue 9, 794 - 803.
- Ruslie, R. H., Darmadi, D., & Siregar, G. A. (2021). Vascular Endothelial Growth Factor (VEGF) and Neopterin Levels in Children with Steroid-sensitive and Steroid-resistant Nephrotic Syndrome. *Medical Archives*, Volume 75, Issue 2, 133 - 137.
- Tanaka, Y., Yamamoto, M., Nozu, K., & Nozu, K. (2023). An 8-month-old boy with infantile nephrotic syndrome caused by semaphorin 3B-associated membranous nephropathy. *CEN Case Reports*, Volume 12, Issue 3, 281 - 286.
- Zhang, F., Wang, H., Bai, Y., Zhang, Y., Huang, L., & Zhang, H. (2023). Prevalence of physical frailty and impact on survival in patients with chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrology*, Volume 24, Issue 1.
- Zhu, X., Zhang, Y., Yu, Z., Yu, L., Huang, W., Sun, S., . . . Deng, F. (2022). The Clinical and Genetic Features in Chinese Children With Steroid-Resistant or Early-Onset Nephrotic Syndrome: A Multicenter Cohort Study. *Frontiers in Medicine*.