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Frequency, Risk Factors and Outcome of Acute Kidney Injury in Idiopathic Childhood Nephrotic Syndrome: A Systematic Review

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Abstract:

Objectives: Idiopathic nephrotic syndrome is a common glomerular disease with a good prognosis in the long term. However, the development of acute kidney injury may complicate the disease course. This systematic review was conducted to evaluate the frequency, risk factors and outcome of AKI in children with idiopathic nephrotic syndrome.

Methods: PubMed, EMBASE, and CENTRAL were systematically searched from January 1974 to July 2024 for retrospective and prospective observational studies. The systematic review was prospectively registered with PROSPERO and written in compliance with PRISMA guidelines. The quality assessment tool was used to evaluate the quality of included studies.

Results: Out of 271 identified studies, 14 were included in the systematic review. Most studies were retrospective in design. The most common risk factors for acute kidney injury in children were infections (sepsis, spontaneous bacterial peritonitis, pneumonia, and urinary tract infections) and nephrotoxic drug exposure (e.g., nephrotoxic antibiotics, renin-angiotensin modifiers, methylprednisolone, and calcineurin inhibitors). Recovery from AKI occurred in 48 – 100% of cases, while chronic kidney disease development ranged from 0 - 41.2% and a maximum reported mortality rate of 23%. The quality assessment through NHLBI rated 85% studies as good.

Conclusion: Acute kidney injury is a relatively frequent and serious complication in children with nephrotic syndrome, often associated with infections and nephrotoxic drug exposure. This systematic review, conducted using a structured approach highlights the need of preventive strategies and further research in this vulnerable population.

Keywords: Nephrotic syndrome, Acute kidney injury, Outcome, systematic analysis, mortality, morbidity.

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Introduction:

Idiopathic nephrotic syndrome (INS) is a common pediatric kidney disease which typically shows a favorable response with corticosteroid therapy.[1] The key diagnostic features are swelling, hypoalbuminemia and nephrotic range proteinuria. Low serum albumin leads to a reduction in

intravascular oncotic pressure and effective circulatory volume. Such altered intravascular milieu predisposes to compromised kidney perfusion and risk of acute kidney injury (AKI).[2] The incidence of AKI in INS is quite variable, ranging from 0.8 to 58.6%.[3] In INS, the leading cause of AKI is primarily pre-renal.[4] Moreover, acute illnesses like vomiting, diarrhea, and sepsis alter the hemodynamics, which worsen the kidney injury. Another often overlooked factor in clinical practice is the exposure to nephrotoxic drugs.[5] Goldstein et al reported that replacement of nephrotoxic with less or non-nephrotoxic drugs led to a reduction in the rate of AKI among hospitalized children by 23%.[6] Therefore, the development of AKI can lead to complications like increased length of hospital stay, a higher risk of chronic kidney disease (CKD) in the long term and increased mortality.[7]

Regarding the outcomes of AKI in INS, Ghosh et al reported that 18% met the AKI criteria defined by pediatric RIFLE, out of them 14% developed acute kidney disease (AKD) and 6% progressed to CKD.[8]

The literature pertaining to this subject exhibit considerable variability, and is further limited by small sample sizes. This review aims to systematically gather the available evidence on frequency, risk factors and outcome of acute kidney injury in children with nephrotic syndrome.

Methods:

The protocol of this systematic review was prospectively registered with PROSPERO (CRD42023439205). We searched Medline through PubMed, EMBASE, and Cochrane with controlled vocabulary of each database and keywords to identify all the relevant studies published in the past five decades from January 1974 to July 2024. The details of the search strategy are mentioned in the supplementary Table 1. We also hand-searched a reference list of review articles, editorials, and conference abstracts to include the additional studies. The citation tracking was carried out on PubMed as well.

All the retrospective, prospective cohort and case control studies were included. While case series, case reports and commentaries were excluded. Studies with children less than 18 years and diagnosed with idiopathic childhood nephrotic syndrome who developed acute kidney injury were included. AKI defined by any of the criteria, like KDIGO, AKIN, and pediatric RIFLE, were eligible for the inclusion.[9] Secondary causes of nephrotic syndrome, like lupus nephritis, membranoproliferative glomerulonephritis, and membranous nephropathy, were excluded.

The parameters of outcome were documented in the form of:

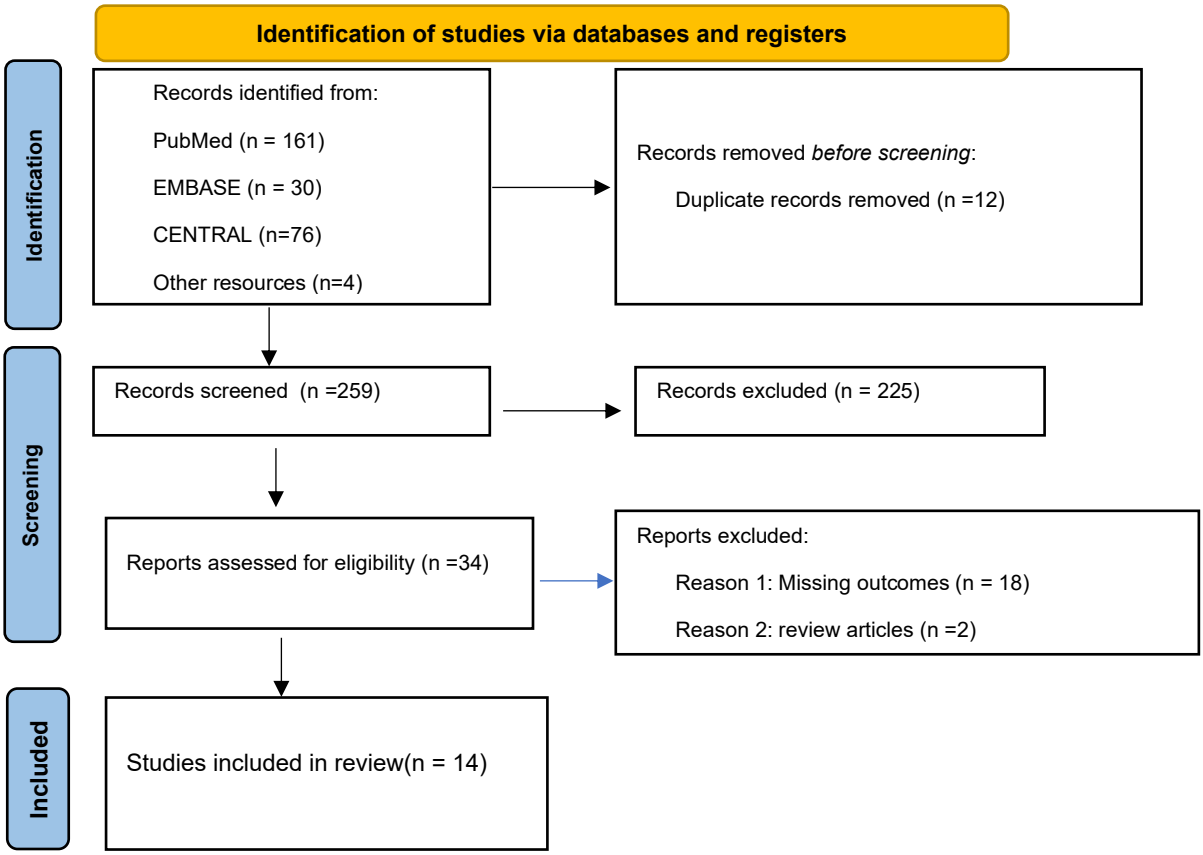
- Frequency, incidence, and prevalence of AKI in nephrotic syndrome
- Risk factors for the development of AKI like hypovolemia, infection, and nephrotoxic drug exposure
- Outcome after the development of AKI, like acute kidney disease, chronic kidney disease, length of hospital stays, end-stage kidney disease, and mortality.

All the articles found through databases and manual search were imported to reference managing software, and duplicates were removed. The title and abstract screening were done by two authors (IA and HQ) to find the potential studies for full text review. The third researcher, who was senior in the team was contacted to resolve the conflicts between two reviewers (AL).

The selected studies fulfilling the inclusion criteria underwent data extraction by two authors, IA and SK, independently. We collected variables in the electronic data sheet like author, study year, country, type of study, age category, type of nephrotic syndrome, criteria of acute kidney injury, risk factors (hypovolemia, infection, and nephrotoxic drug exposure) and outcome of AKI (length of hospital stay, acute kidney disease, chronic kidney disease, end-stage kidney disease and mortality).

The meta-analysis of proportion was planned initially, but due to heterogeneous data, it could not be performed. Risk of bias in the individual studies was detected through the National Heart, Lung, and Blood Institute (NHLBI) tool for observational cohort and cross-sectional studies.[10] This tool has 14 questions with answers coded as yes, no, cannot determine, not reported, and not applicable. Two authors (IA and SK) separately evaluated all the studies and later discussed with the senior author (AL) to resolve the conflicts. We undertook a percentage of questions with "yes" answers and excluded not-applicable items. The quality rating of good, fair, and poor was categorized based on scores of >75%, 50-75 %, and < 50%.

Figure 1. Flow chart demonstrating the selection of studies



Results:

We identified 271 studies across the databases, of which 12 were removed due to duplication and 259 underwent screening based on title and abstract. Later, 34 studies were considered eligible for the full text review.[11-32] Another twenty records were excluded based on the reasons mentioned in the Figure 1.

Finally, 14 studies entered the systematic review phase. Table 1 describes the baseline details of all the studies. Among the included 14 studies, one study by Yaseen et al had enrolled only children with AKI.[23] Most of the studies were retrospective in design 9 (64%). The frequency of AKI varied from 3.6 to 58.6 % in retrospective studies, and incidence was reported as 9.8 to 42.6 % in prospective observational studies as shown in Figure 2.

The most common risk factors for the development of AKI were infection and exposure to nephrotoxic drugs. The spectrum of infection included sepsis, spontaneous bacterial peritonitis, pneumonia, and urinary tract infection. The studies included in the analysis revealed nephrotoxic antibiotics, renin angiotensin modifiers, methylprednisolone, and calcineurin inhibitors as the offending agents. Table 2 outlines the risk factors mentioned in each study.

Table 1: Baseline characteristics of the included studies

Year/Author	Country	Study design	AKI definition	Age(Meanor Median)/Male
2015/Rheault (22)	USA	Retrospective	pRIFLE	--/63.4%
2017/Yaseen (23)	Pakistan	Prospective	pRIFLE	8.8±3.59/62.2%
2018/Kim (24)	South Korea	Retrospective	KDIGO	7.8 (4.4 – 14.3)/65.5 %
2018/Sharma (3)	India	Retrospective	pRIFLE	--/65%
2019/Kushwah (25)	India	Prospective	KDIGO	5.3 (4 – 9.2)/72.2%
2019/Prasad (26)	India	Prospective	KDIGO	AKI 5 (3-7.6) and NON-AKI 4.2 (3-8)/55.5%
2021/Sato (27)	Japan	Retrospective	KDIGO	4.5 (2.8 - 9.4)/67%
2021/Kumar (17)	India	Prospective	pRIFLE KDIGO	4.9/64.8%
2021/ Guan (28)	China	Retrospective	pRIFLE	8.3(2-16) /67.6%
2021/ Yang (29)	South Korea	Retrospective	KDIGO	5.8 (3.1 - 7.7)/72.9%
2022/Anigilaje (30)	Nigeria	Retrospective	pRIFLE	10±18/85.3%
2023/Ghosh (8)	India	Prospective	pRIFLE KDIGO	4 (3 – 7)/37%
2023/Uma (31)	India	Prospective	KDIGO	4.08±4.04/60%
2024/Khichar (32)	India	Retrospective	KDIGO	7.23±5.62/ 67.2%

The children with nephrotic syndrome and acute kidney injury had a variable length of hospital stay. The AKI recovered in 48 to 100% of children, and the development of any stage of CKD was reported in 0 to 41.2%. The maximum mortality rate was described by Prasad et al at 23%. The outcome of all the studies is shown in Table 3.

Table 2: Risk factors for the development of Acute Kidney Injury

Author/Year	Risk factors
2015/Rheault (22)	Infection, nephrotoxic medication exposure, days of nephrotoxic medication exposure, and intensity of medication exposure
2017/Yaseen(23)	Infection, sepsis, hypovolemia, and nephrotoxic drugs
2018/ Kim (24)	Infection, nephrotic syndrome aggravation, dehydration, intravenous methylprednisolone administration, age ≥ 9 years at admission, and combined use of cyclosporine and renin-angiotensin system inhibitors were risk factors for AKI.
2018/Sharma (3)	Infections and nephrotoxic medication exposure
2019/Kushwah (25)	Steroid resistance, low serum albumin, and eGFR at admission
2019/Prasad (26)	Steroid resistance, hypovolemic shock, peritonitis, exposure to ACE inhibitors, and furosemide infusion
2021/Sato (27)	Female gender and hypertension
2021/Kumar (17)	Infection, low hemoglobin, and ACEI use
2021/ Guan (28)	Infections, hypovolemia, CNI, ACEI, and nephrotoxic antibiotics
2021/Yang (29)	Longer disease duration, lower albumin level, and methylprednisolone pulse treatment
2022/Anigilaje (30)	Sepsis, nephrotoxic drugs, and hematuria
2023/Ghosh	Fractional excretion of sodium, male gender, underlying infection, nephrotoxic drugs, and albumin
2023/Uma (31)	Infection and nephrotoxic drugs
2024/Khichar (32)	Sepsis, acute respiratory distress syndrome, nephrotoxic medications, renal parenchymal disease, post-streptococcal glomerulonephritis, Sickle cell disease with nephritis and acute fulminant hepatitis

Table 3: Outcome reported in the included studies

Year/Author	Sample size	CKD/ESKD	Mortality	RRT	LOS (Days)
2015/Rheault (22)	336 with 615 hospitalizations	--	1	2	1.73±0.63 (Log)
2017/Yaseen (23)	119 with AKI	49	5	--	--
2018/Kim (24)	65 with 90 hospitalizations	--	0	0	12 (5.5-19)
2018/Sharma (3)	355	--	0	0	--
2019/ Kushwah (25)	115	10	3	--	7 (5-14)
2019/Parsad (26)	73 with 81 hospitalizations	3	3	1	16 (12-24)
2021/Sato (27)	999	1	2	4	--
2021/Kumar (17)	44	0	0	0	12.6 ± 5.4
2021/Guan (28)	59 with 68 hospitalizations	2	0	7	--
2021/Yang (29)	363 with 574 hospitalizations	6	0	--	10 (6-16)
2022/Anigilaje (30)	75	1	2	4	--
2023/Ghosh (8)	176 with 200 hospitalizations	2	1	2	13.6 ± 4.6
2023/Uma (31)	304	4	2	7	19.1 ± 11 (SRNS) and 15.2 ± 6.84 (SSNS)
2024/Khichar (32)	64	--	2	--	6.40 ± 4.41

CKD= Chronic kidney disease, ESKD= End stage kidney disease, RRT= Renal replacement therapy, LOS= Length of hospital stay, SSNS=Steroid sensitive nephrotic syndrome and SRNS=Steroid resistant nephrotic syndrome

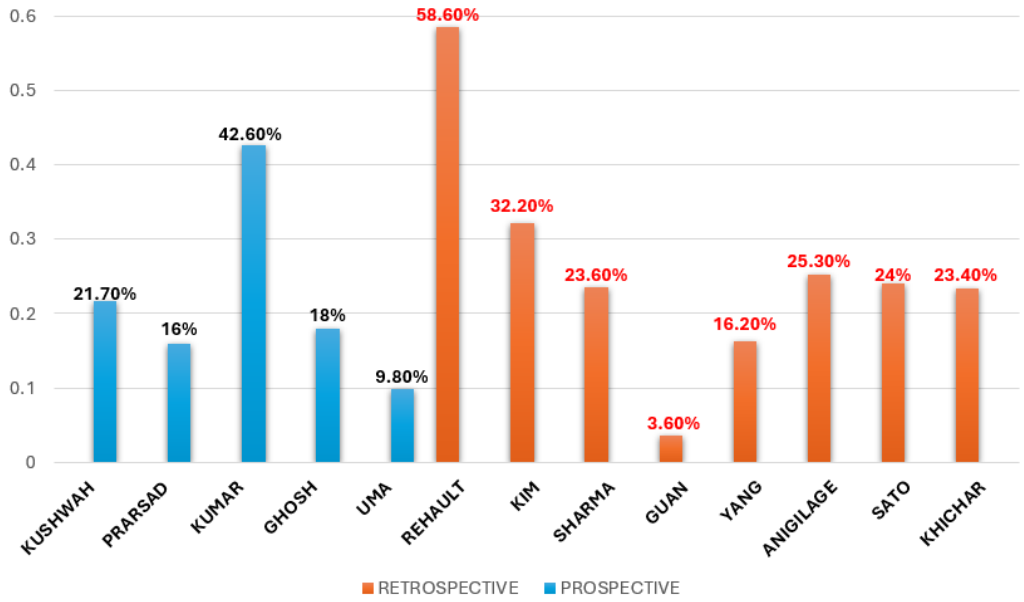
The quality assessment revealed that most of the studies 12 (85%) were of good quality, 2 (14%) fair and none of the studies was rated poor. The details are shown in the supplementary Table 2. Items 8, 10 and 12 in the NHLBI tool were consistently not applicable to any of the study.

Discussion:

The primary finding of this systematic review demonstrates the notable development of AKI in children with INS. It leads to poor outcomes during disease, in terms of length of hospital stay, delayed recovery, requirement of kidney replacement therapy, and mortality.

AKI is the third most common complication in children hospitalized with nephrotic syndrome.[11] A study from Poland in 2000 reported the frequency of AKI as 0.8% in 1006 hospitalized children.[12] Rheault et al conducted a study using the Healthcare Cost and Utilization Project Kids Inpatient Database and documented an increase of 158% in AKI from 2000-2009.[13] This surge in AKI frequency may be attributed to the evolution of AKI definitions in children over the years. Therefore, prospective studies with current definitions of AKI are required to accurately determine its frequency in this high-risk population.

Figure 2. The frequency of AKI in the included studies



The estimation of the true frequency of AKI may be challenging in INS. In clinical practice, serum creatinine and urinary volume help in the determination of kidney function. However, in the context of AKI in nephrotic syndrome, both become unreliable, as serum creatinine has inherent limitations and hypoalbuminemia predisposes to oliguria.[14] Recent efforts have focused on identifying novel biomarkers

like NGAL and KIM-1 as potential parameters in INS.[15] Both can help in distinguishing between acute tubular necrosis and glomerulonephritis, which is the main concern for treating physicians.

Infections in INS are the vital risk factors for the development of AKI.[16] Our review identified spontaneous bacterial peritonitis, pneumonia, urinary tract infection, and sepsis in INS as the predominant etiologies predisposing to AKI. Kumar et al identified similar spectrum of infections in children with nephrotic syndrome.[17] This highlights the importance of vaccinations in children with INS to prevent the development of pneumococcal and influenza infections.[18]

Multiple drugs are advised in INS, like steroids, angiotensin converting enzyme inhibitors, calcineurin inhibitors, and various antibiotics for treating infections.[19] Most of these agents have deleterious adverse effects on kidney function. Sato et al found Methylprednisolone as risk factor for AKI, which may be attributed to increased sodium and water retention with concomitant interstitial edema.[20] The drug dose and duration of therapy are related to the burden of AKI in INS. Similarly, parental counselling regarding discontinuation of potential nephrotoxic drugs during infections is warranted. Physicians should consider the judicious use of nephrotoxic antimicrobials during an infection episode.

Ghosh and Sato et al identified male and female sex as the risk factor of AKI respectively.[8,27] However, given the limited number of studies addressing this association, it cannot be attributed as causal factor. Key prognostic features of AKI in INS are length of hospital stay, development of chronic kidney disease, end-stage kidney disease, and mortality. All of these are emphasized in our review. Additionally, AKI in hospitalized patients is independently associated with higher mortality and length of hospital stay.[21]

Our results highlight several issues with important implications for future studies. Majority of the studies included in the systematic review were published in the last decade. Yet the definitions of AKI used were variable and important outcomes were not consistently identified. The identification of these factors can generate valuable data in future systematically conducted review.

The pooled estimates in the meta-analysis were not attempted. The clinical heterogeneity was evident with different classifications of AKI, and there was no uniformity in reporting the severity of AKI. As we tried to generate the pooled estimate of AKI and other outcome measures, we found statistical heterogeneity among the included studies. Moreover, the outcome of AKI was not uniformly reported across the included studies. In the presence of these limitations, the gravity of the issues identified by this review cannot be disregarded. The risk of bias through the NHLBI tool showed that most of the studies were at low risk.

This systematic review highlights the significant burden of AKI in children with INS, emphasising its association with poor clinical outcomes. The variability in the definition of AKI and outcome reporting suggests the standardized criteria in future research.

Conclusion:

- Idiopathic nephrotic syndrome predisposes to AKI with an incidence ranging from 0.8% to 58.6%.
- Key risk factors for AKI include infections and nephrotoxic drug exposure.
- AKI in nephrotic syndrome increases hospital stay, CKD risk, and mortality.

Disclosures/Conflict of Interest:

Authors declare no conflict of interest

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Supplementary Table 1. Search strategy of the systematic review

Database	Search Strategy *ran on 05/07/2024*
PubMed	Search: (((((((epidemiology [MeSH] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter]))) OR (epidemiology[Subheading] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter])))) OR (prevalence [MeSH] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter])))) OR (incidence [MeSH] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter])))) OR (frequency [All fields] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter])))) OR (risk factors [MeSH] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter]))) AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter]))) AND (Renal Insufficiency[MeSH] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter])))) AND (nephrotic syndrome [MeSH] AND ((1974/1/1:2024/7/5[pdat]) AND (english[Filter]) AND (allchild[Filter]))) **Filters:** English, Child: birth-18 years, from 1974/1/1 - 2024/7/5 Filters: English, Child: birth-18 years, from 1974/1/1 - 2023/10/9 #1 - epidemiology [MeSH] 4101 #2- epidemiology[Subheading] 691,281 #3 - prevalence [MeSH] 118,289 #4 - incidence [MeSH] 85,584 #5- frequency [All fields] 857,353 #6 - risk factors [MeSH] 220,075 #7 - #1 OR #2 OR #3 OR #4 OR #5 OR #6 943,272 #8- Renal Insufficiency[MeSH] 22,372 #9 - nephrotic syndrome [MeSH] 5,470 #10 - # 7 AND #8 AND #9 161
EMBASE	1 ('Idiopathic Childhood Nephrotic Syndrome' or 'pediatric Idiopathic Nephrotic Syndrome' or 'paediatric Idiopathic Nephrotic Syndrome').m_titl. 50 2 ('Idiopathic Nephrotic Syndrome' adj3 (child* or pediatric or paediatric)).m_titl. 633 3 Nephrotic Syndrome/ 35166 4 limit 3 to child 9147 5 1 or 2 or 4 9273 6 acute kidney injury.m_titl. 28363 7 5 and 6 48 8 conference.so,pt. 5989954 9 7 not 8 30
CENTRAL	(epidemiology OR prevalence OR incidence OR frequency OR risk factors) AND ("acute kidney injury" OR "acute renal failure" OR "acute renal insufficiency") AND ("nephrotic syndrome") OR (primary childhood nephrotic syndrome) OR (idiopathic childhood nephrotic syndrome) in Title Abstract Keyword Trials - 76

Supplementary Table 2. Risk of Bias in selected studies
Codes: Yes 1, No 2, Can't determine 3, not reported 4 and not applicable 5

Year/ Author	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	over all
2015/Rheault	1	1	1	1	2	1	1	5	1	5	1	5	1	1	81%
2017/Yaseen	1	1	4	1	2	1	1	5	1	5	1	5	1	2	72%
2018/Kim	1	1	1	1	2	1	1	5	1	5	1	5	1	1	91%
2018 Sharma	1	1	1	1	2	1	1	5	1	5	1	5	1	1	91%
2019/ Prasad	1	1	1	1	1	1	1	5	1	5	1	5	1	1	100 %
2019/Kushwah	1	1	1	1	1	1	1	5	1	5	1	5	1	1	100 %
2021/Sato	1	1	1	1	2	1	1	5	1	5	1	5	1	1	91%
2021 /Guan	1	1	1	1	2	1	1	5	1	5	1	5	1	1	91%
2021/Kumar	1	1	1	1	2	1	1	5	1	5	1	5	1	2	82%
2021/Yang	1	1	1	1	2	1	1	5	1	5	1	5	1	1	90%
2021 /Anigilage	1	1	1	2	2	1	1	5	1	5	1	5	1	2	73%
2023 /Ghosh	1	1	1	1	2	1	1	5	1	5	1	5	1	1	90%
2023 /Uma	1	1	1	1	1	1	1	5	1	5	1	5	1	1	100 %
2024/Khichar	1	1	1	1	1	1	1	5	1	5	1	5	1	2	91%