KRACC: KRA COVID Cohort

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The Karnataka Rheumatology AIRD Cohort Collaboration (KRACC) was KRA's COVID cohort study, initiated and executed during the COVID-19 pandemic by practicing rheumatologists from Karnataka. As with many other collaborative research initiatives from KRA, the concept of KRACC emerged in response to real-world challenges faced during this unprecedented time.

At the onset of the COVID-19 pandemic, there was widespread concern and panic among patients with autoimmune rheumatic diseases (AIRD) that they would be more susceptible to severe infection and increased mortality. However, it quickly became apparent that the primary cause of mortality in COVID-19 was an overactive immune response, leading to a Cytokine Storm. This observation led to the hypothesis that patients with AIRD might be somewhat protected against virus-induced hyperinflammatory damage, due to their treatment with immunomodulatory drugs such as hydroxychloroquine and glucocorticoids.

With these objectives in mind, we initiated the Karnataka Rheumatology AIRD Cohort Collaboration (KRACC) to address these questions by longitudinally following patients with autoimmune rheumatic diseases (AIRD) who are receiving immunosuppressive therapy. Rheumatologists from Karnataka, along with one centre from Kerala, participated in this study. A virtual harmonisation meeting was conducted across all participating centres to ensure consistency in data collection. A consensus-driven, structured, and computerized record form was developed to capture all relevant data, enabling physician assistants or research nurses, in addition to the rheumatologists, to collate the information effectively. The data collected included details on COVID-19 exposure, symptoms, virus test results, and outcomes during the initial phase of the pandemic. As subsequent waves of COVID-19 emerged, the questionnaire was expanded to gather information on vaccination, hospitalisation, and outcomes. The follow-up period initially spanned 6 months but was later extended to 12 months.

Challenges: This was one of the most challenging studies undertaken by the KRA group. Public reluctance to disclose symptoms or test results, driven by the stigma associated with COVID-19 and the restrictions on movement, posed significant obstacles. Patients found it difficult to reach their rheumatologists due to lockdowns and restricted travel across states. Additionally, during this period, India was overwhelmed by a rapidly increasing number of COVID-19 cases, with most hospital resources and personnel efforts redirected to managing the crisis. As rheumatologists were not the primary caregivers for COVID-19 patients, we faced difficulties in accessing precise information related to oxygen therapy, hospitalisation, and ICU care.

Despite our determination to push forward beyond our personal experiences with COVID, we faced significant barriers as the infrastructure around us began to shut down. Ethics Committees ceased operations, research teams were sent back to their home states post-

lockdown, and publishers temporarily closed their doors. Nevertheless, a dedicated research team from St. John's maintained consistent follow-up with patients and issued regular reminders to all participating centers to ensure the rigorous collection of necessary data. The information gathered by physician assistants and/or nurses was carefully verified by the respective rheumatologists to ensure accuracy.

This collaborative effort demonstrated the potential for conducting meaningful research with minimal resources, even within private clinic and corporate hospital settings, by focusing on well-framed research questions. As a result of this collective endeavor, we successfully achieved four indexed publications and produced several abstracts.

Publications:

1. *Shobha, Vineeta; Chanakya, K; Haridas, Vikram; Kumar, Sharath; Chebbi, Pramod; Pinto, Benzeeta; Jain, Vikramraj; Ramaswamy, Subramaniam; Prasad, Shiv; Patil, Abhishek; Rao, Vijay K; Yathish, GC; Dharmanand, BG; Jois, Ramesh; Kamath, Ashwini; Dharmapalaiah, Chethana; Sangeeta, KN; Janardana, Ramya; Srinivasa, C; Harshini, AS; Srinivasulu, Nagaraj; Singh, Yogesh Preet; Singhai, Shweta; Mahendranath, KM; Chandrashekara, S. Do all Patients with Rheumatic Diseases have a Higher Risk of COVID 19? Initial Results from the Karnataka Rheumatology Association COVID 19 Cohort Study (KRACC). Indian Journal of Rheumatology 16(2):p 164-S168, June 2021. | DOI: 10.4103/injr.injr_261_20*

Our first paper from KRACC was sent for publication to IJR as early as the end of Aug 2020, which included data from 3807 patients with AIRD between March to August 10, 2020. This manuscript explored the initial impact of COVID-19 and its risk factors in patients with AIRD. By this report, only 23 patients (0.6%) tested positive for COVID-19, a rate comparable to the general population and the majority of infected patients were older and had comorbidities such as diabetes and hypertension. Preexisting lung disease and higher glucocorticoid dosage were identified as significant risk factors. Hydroxychloroquine prescription was common in the cohort (55.2%), but it was not associated with a reduced risk of COVID-19 infection. Of 23 patients with COVID, 65.2% of COVID-19-infected patients were hospitalized, and 3 patients (13%) required intensive care. Three patients succumbed to COVID-19, all of whom had significant comorbidities, including diabetes, lung disease, or a history of cancer.

So, this study provided initial information telling us about risk factors which held true till the end of COVID 19 outbreak. Unfortunately, this work didn't see the light of day till next year as our publishers were not geared up for COVID times.

2. *Patil A, Chanakya K, Shenoy P, Chandrashekara S, Haridas V, Kumar S, Daware M, Janardana R, Pinto B, Subramanian R, Nagaraj S, Singh YP, Singhai S, Jois R, Jain V, Srinivasa C, Dharmanand BG, Dharmapalaiah C, Sangeetha KN, Rao VK, Shobha V. A prospective longitudinal study evaluating the influence of immunosuppressives and other factors on COVID-19 in autoimmune rheumatic diseases. BMC Rheumatol. 2022 Jun 14;6(1):32. doi: 10.1186/s41927-022-00264-0. PMID: 35698182; PMCID: PMC9192133.*

This manuscript included patients not only from Karnataka but also from Kerala. Of 9212 AIRD patients, 314(3.45%) contracted COVID-19 over a median follow up period of 6 months. This incident rate was 3 times compared to the general population. The case fatality rate among AIRD patients was 4.1%, compared to 1.3% in the general population, suggesting a considerably higher risk for these patients. Key risk factors included older age, male sex, diabetes, smoking, and pre-existing lung diseases. We were also able to reject the protective effect of HCQ on COVID 19 occurrence and severity. Moderate doses (7.5–20 mg/day) of glucocorticoids increased the risk of infection, however, the use of high doses showed a potential risk without conclusive evidence on mortality.

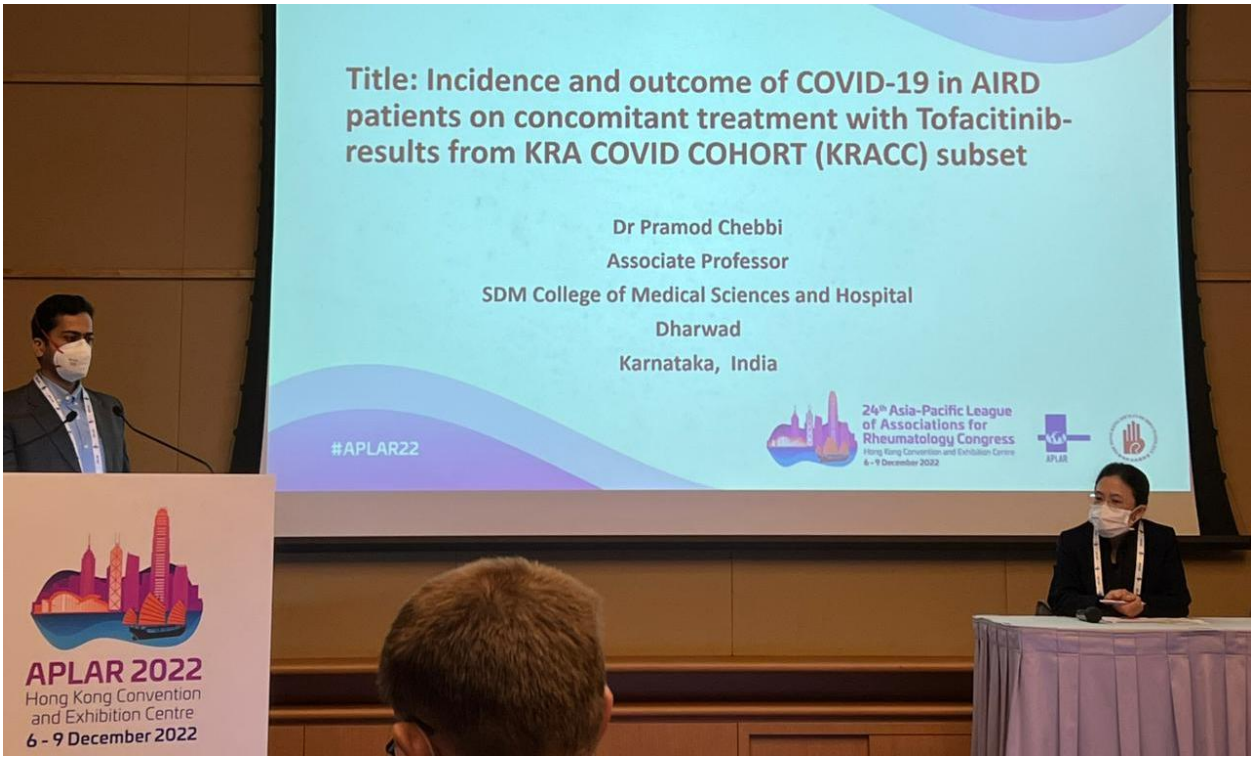
3. *Chebbi P, Shobha V, Rao VK, Haridas V, Janardana R, Pinto B, Kumar S, Patil A, Tekkatte R, Salanke M, Mahendranath KM. Occurrence and outcome of COVID-19 in AIRD patients on concomitant treatment with Tofacitinib- results from KRA COVID COHORT (KRACC) subset. BMC Rheumatol. 2023 Jul 26;7(1):22. doi: 10.1186/s41927-023-00345-8. PMID: 37496101; PMCID: PMC10369741*.

This analysis was carried out in the latter half of COVID epidemic (June-July 2021) when JAK inhibitors such as tofacitinib were used as treatment of moderate-severe COVID. Here, we were curious to understand about the incidence and severity of COVID-19 in patients who were already on treatment with tofacitinib for their arthritis.

Of 335 patients on current prescription of tofacitinib, 10.7% (36/335) contracted COVID-19. This infection rate was higher than the general population (4.3%) during the same period and higher than AIRD patients not on tofacitinib. Here again, diabetes was identified as a significant risk factor for COVID-19. To our surprise, methotrexate was associated with a lower incidence of COVID-19 (OR 0.46, $P = 0.04$). The majority (91.2%) of infected patients recovered. However, three patients (8.33%) succumbed, all of whom had comorbidities such as diabetes, hypertension, or obesity.

By the time of this study, COVID vaccination was in place. Approximately half of the cohort (52%) had received at least one dose of the COVID-19 vaccine. Vaccination significantly reduced the incidence of COVID-19 in the cohort (OR 0.15, $P < 0.0001$). None of the patients who died had received the vaccine, highlighting the protective role of vaccination

This paper was presented on the Oral platform at APLAR-22 in Hong Kong by Dr Pramod Chebbi. (pic below)



4. *Jain V, Shobha V, Kumar S, Janardana R, Selvam S. Comparison of Risk Factors During First and Second Wave of COVID-19 in Patients with Autoimmune Rheumatic Diseases (AIRD): Results from KRACC Subset. Mediterr J Rheumatol. 2023 Aug 27;34(3):342-348. doi: 10.31138/mjr.20230827.co. PMID: 37941863; PMCID: PMC10628883.*

This study focused on comparing the impact of several risk factors on the occurrence of COVID-19 during the first and second waves (delta variant) of the COVID-19 pandemic among patients with AIRD. Data was collected from patients during the first wave (up to December 2020) and the second wave (January to August 2021). This analysis revealed a significantly higher incidence of COVID-19 among AIRD patients during the second wave (7.1%) compared to the first wave (1.7%); the mortality rate was also slightly higher during the second wave. Older age and longer duration of AIRD were associated with a higher occurrence and mortality. Further, diabetes mellitus was independent risk factors for COVID-19-related mortality during the second wave.

The study collected data on COVID-19 vaccination during the second wave, finding that 61.3% of patients had received at least one dose by August 2021, and a smaller percentage contracted COVID-19 after vaccination. This paper was presented as an Oral abstract (virtually) during APLAR 2022 at Hong Kong by Dr Vikram Raj Jain. (pic below)

Title	Utility of Tofacitinib beyond Autoimmunity
Paper Number	792
Presentation type	Poster presentation
Presentation details	Digital poster presentation submission deadline Monday, Oct 31, 2022 11:00 PM -
Title	Risk factors associated with COVID 19 in Systemic Lupus Erythematosus: Results from a longitudinal prospective cohort
Paper Number	862
Presentation type	Poster presentation
Presentation details	Digital poster presentation submission deadline Monday, Oct 31, 2022 11:00 PM -
Title	Comparison of risk factors during first and second wave of COVID-19 in patients with Autoimmune Rheumatic diseases(AIRD)-results from KRACC subset
Paper Number	869
Presentation type	Oral presentation
Presentation details	Oral abstract session 4 Thursday, Dec 8, 2022 8:00 AM - 9:00 AM
Speaker notes	Presentation length will be 6 minutes excluding Q&A, you will have an additional 2 minutes for questions.

5. *Patil A, Shobha V, Shenoy P, S C, Kumar S, Daware M, Haridas V, Janardana R, Pinto B, Kodishala C, Ramaswamy S, S N, Jain V, Singh YP, Singhai S, Chandrashekara S, Jois R, Rao VK, Dharmapalaiah C, KN Sangeeta, Balebail D. Risk factors associated with COVID-19 in systemic lupus erythematosus: Results from a longitudinal prospective cohort. Lupus. 2023 Apr;32(4):560-564. doi: 10.1177/09612033231155837. Epub 2023 Feb 2. PMID: 36731873; PMCID: PMC9899665*.

This was a subanalysis of our main KRACC cohort which included 9212 patients with AIRD, conducted between April–December 2020. Out of 1379 patients with SLE in KRACC, 36(2.9%) developed COVID-19. On analysing the COVID-19 positive versus negative, male gender and diabetes emerged as the strongest risk factors for COVID-19. There was no significant influence of organ involvement, medications such as hydroxychloroquine, glucocorticoid dosage or category of other immunosuppressants on the risk of COVID-19. There was only one death (1/36) among the lupus patients due to COVID-19. We concluded that traditional risk factors rather than lupus disease process or IS influenced the risk of COVID-19 in our cohort.