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Details of papers published in the journals notified on UGC – CARE list in the UGC website 2022

S.N	UGC website/ Scopus/ Web of Science/ PubMed	Publication type	Publication title	Author name	Journal name	Year
1.	Scopus, Web of Science	Original article	Determinants of health-related quality of life in south Indian patients with rheumatoid arthritis: A structural equation modeling approach	Trupti Bodhare, Samir Bele, Subramanian Nallasivan1, J. Vijay Anto	Indian Journal of Rheumatology	2022
2.	35464571	Original article	The Prevalence of Reproductive Tract Infections Based on the Syndromic Management Approach Among Ever-Married Rural Women in Kancheepuram District, Tamil Nadu: A Community-Based Cross-Sectional Study	Balakrishnan S, Carolin A, B Sudharsan, R Shivasakthimani	Cureus	2022
3.	35497703	Original article	Opioid-free anaesthesia for laparoscopic surgeries - A prospective non-randomised study in a tertiary care hospital	Ragupathy R, Prabhu SCG, Thiyagarajan D, Anto V	Indian Journal of Anaesthesia	2022
4.	Scopus	Original article	Determinants of health-related quality of life in south indian patients with rheumatoid arthritis: A structural equation modeling approach	Trupti Bodhare, Samir Bele, Subramanian Nallasivan, Vijay Anto J	Indian Journal of Rheumatology Assotiation	2022

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5.	33723658	Original article	Clinical features, severity and outcome of acute pancreatitis in systemic lupus erythematosus	Muhammed H, Jain A, Irfan M, Charles S, Dwivedi P, Chavan PP, Khubchandani R, Sharma A, Phatak S, Shukla AN, Shah R, Subramanian N, Pandya SC, Singh YP, Chengappa KG, Thabah M, Rajasekhar L, Shobha V, Negi VS, Dhir V, Sharma A, Misra R, Aggarwal A; SLE-SIG of IRA	Rheumatology International	2022
6.	SCOPUS, Web of Science	Original article	Prospective study of patients with inflammatory back pain, clinical characteristics and treatment response in ankylosing spondylitis in two centers of rheumatology in South India	Subramanian Nallasivan, Dhivya Thiyagarajan, Abirami Manivannan	Indian Journal of Rheumatology	2022
7.	35940463	Original article	Masked right bundle branch conduction delay pattern during left bundle branch pacing	Vijayaraman P, Ponnusamy SS	Heart rhythm	2022
8.	35715077	Review article	Evaluation of Criteria for Left Bundle Branch Capture	Ponnusamy SS, Vijayaraman P	Cardiac electrophysiology clinics	2022
9.	35695790	Original article	M-beat-A novel marker for selective left bundle branch capture	Ponnusamy SS, Basil W, Vijayaraman P	Journal of cardiovascular electrop	2022

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10.	3550453 9	Origina l article	Rescue left bundle branch area pacing in coronary venous lead failure or nonresponse to biventricular pacing: Results from International LBBAP Collaborative Study Group.	Vijayaraman P, Herweg B, Verma A, Sharma PS, Batul SA, Ponnusamy SS, Schaller RD, Cano O, Molina-Lerma M, Curila K, Huybrechts W, Wilson DR, Rademakers LM, Sreekumar P, Upadhyay G, Vernooy K, Subzposh FA, Huang W, Jastrzebski M, Ellenbogen KA	Heart rhythm	2022
11.	3533143 9	Origina l article	Left Bundle Branch Optimized Cardiac Resynchronization Therapy in Mesocardia With Bilateral Superior Vena Cava	Ponnusamy SS, Syed T, Basil W	JACC: Clinical Electrop hysiolog y	2022
12.	3506618 0	Origina l article	Response of functional mitral regurgitation in nonischemic cardiomyopathy to left bundle branch pacing	Ponnusamy SS, Syed T, Vijayaraman P	Heart rhythm	2022
13.	3506617 8	Origina l article	Electrophysiological characteristics of septal perforation during left bundle branch pacing	Ponnusamy SS, Basil W, Vijayaraman P.	Heart rhythm	2022
14.	3498564 2	Case Report s	Double transition sign-a marker of left bundle branch capture during physiological pacing	Ponnusamy SS	Journal of interven tional cardiac electrop hysiolog y : an	2022

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15.	34921478	Original article	Axis deviation in nonischemic cardiomyopathy with left bundle branch block: Insights from left bundle branch pacing.	Ponnusamy SS, Vijayaraman P	Journal of cardiovascular electrophysiology	2022
16.	34339851	Original article	Left bundle branch-optimized cardiac resynchronization therapy (LOT-CRT): Results from an international LBBAP collaborative study group	Jastrzębski M, Moskal P, Huybrechts W, Curila K, Sreekumar P, Rademakers LM, Ponnusamy SS, Herweg B, Sharma PS, Bednarek A, Rajzer M, Vijayaraman P	Heart rhythm	2022

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Indian Journal of RHEUMATOLOGY

ORIGINAL ARTICLE
Ahead of print publication

Determinants of health-related quality of life in south indian patients with rheumatoid arthritis: A structural equation modeling approach

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Abstract

Introduction: The burden associated with rheumatoid arthritis (RA) is substantial, leading to pain, suffering, impaired physical function, disability and deterioration in quality of life of the patients. Very few studies evaluating health-related quality of life (HRQOL) and its determinants have been published among RA patients in Southern India. The aim of the present study is to investigate the various dimensions of HRQOL and its relationship with various sociodemographic characteristics, functional status and disease activity using a structural equation modeling (SEM) approach in patients with RA.
Materials and Methods: A cross-sectional study was conducted among 110 patients attending tertiary care teaching hospital. SF 36 was used to assess the HRQOL. Disease activity score-28 (DAS28) was used to measure the disease activity and Health Assessment Questionnaire Disability Index (HAQ-DI) was used for measurement of functional disability. SEM analysis was performed to test and evaluate the structural relationships of the model using R Programming.
Results: The mean age of patients was 44.85 ± 11.25 years and 92 (83.6%) were female. Lower HRQOL scores were obtained in the domain of role functioning/physical 48.86 (±40.55), general health 48.27 (±14.92) and physical functioning 40.45 (±23.76). SEM results showed that HAQ–DI and DAS28 were covariance with each other (r = 0.54, P = 0.039), HAQ-DI was a significant predictor of GenPHYS (P = 0.001) and DAS28 was a significant predictor of GenPHYS (P = 0.001) and GenMENT (0.025).
Conclusions: Impact of RA was substantial in both physical and mental domains of HRQOL. The functional disability was having an impact on physical health, whereas disease activity was associated with physical and mental health

domains of HRQOL.

Keywords: *Disease activity score 28, HAQ-DI, health-related quality of life, rheumatoid arthritis, structural equation modeling*

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Introduction

Rheumatoid arthritis (RA) is a chronic, symmetric polyarthritis causing joint damage that inevitably progressed to disability. The disease takes its toll on functional status of the patient leading to impaired physical function, and deterioration in quality of life. The public health burden associated with RA is substantial, including pain, suffering, increased health care utilization, significantly impacting the patients and their families.[1]

The health-related quality of life (HRQOL) is a multi-dimensional and subjective construct which includes the perception of a person's physical, psychological, social, and spiritual well-being in the context of their health conditions and treatment outcomes.[2] It is one of the powerful predictors of morbidity and mortality and is increasingly recognized as a crucial outcome in clinical practice and research. It has become a valid indicator of measuring the quality of health care delivery and treatment outcomes and shall be an integral part of health surveillance for better monitoring of disease burden especially in chronic diseases like RA. Its evaluation shall become a part of everyday clinical practice assessing the influence of disease and focusing on comprehensive care incorporating the bio-psycho-social aspect of a patient's health.[3],[4]

Several instruments have been developed to assess the quality of life and can broadly be categorized into global, generic, and disease-specific instruments.[5]

Studies have shown that there are several factors like socio-demographic, clinical, and psychosocial factors which affect all the aspects of the HRQOL. Age, gender, level of education, socioeconomic status (SES) showed an association with HRQOL.[6] Similarly, several diseases related factors like articular and extra-articular manifestations, disease activity, and functioning impairment, affect HRQOL adversely. Regular assessment of disease activity is crucial for the management of RA and instrument like disease activity score-28 (DAS28) is available for the assessment. However, the utility of DAS28 in evaluation of the disease activity has been grossly neglected in India.[4],[7]

Globally, around 3.4 million (95% UI 2.6–4.4) DALYs are attributed to RA and there is a significant increase in rates in the recent years.[8] In India, RA is predominantly affecting the rural areas and younger women. Limited data are available on evaluation of the overall burden of RA, and HRQOL significantly impacting the quality of care to such patients.[9]

There is an unmet need to sensitize the healthcare providers to understand the importance of various aspects of quality of life of patients suffering from RA and its correlates which will help them in predicting the course of illness and better monitoring of disease burden to plan and intervene to improve overall wellbeing of patients. Similarly, very few studies evaluating HRQOL among RA patients have been conducted in India especially in the southern part. Considering the epidemiological diversity within the country, the present study was aimed to investigate the various dimensions of HRQOL and its relationship with various demographic and clinical parameters, functional status and disease activity using a structural equation modeling (SEM) approach in RA patients attending the tertiary care hospital in south India.

Materials and Methods

Study design and setting

A hospital based cross-sectional study was conducted during October 2020–September 2021 among patients attending the rheumatology clinic, department of General Medicine of a tertiary care teaching institute.

Participants

The study sample consisted of patients having age >18 years, suffering from RA diagnosed by a Rheumatologist as per the American College of Rheumatology/European League Against Rheumatism 2010 criteria for RA classification.[10] Patients having co-morbid conditions, critically ill, pregnant females and patients not willing to participate were excluded from the study. A total of 110 patients participated in the study through convenient sampling. The approval from the Institutional Ethics Committee of the Institute was obtained before the starting the data collection (IEC approval No: VMCIEC/37/2019, Dated: September 18, 2019). The purpose of the study and nature of questions were explained to the patients and written informed consent was obtained.

Data sources/measurement

A semi-structured questionnaire was administered to the patients which consisted of socio-demographic characteristics, clinical parameters and medication details. The Medical Outcomes Study Short-Form Health Survey (SF-36) was used to

assess the HRQOL, DAS28 was used to measure the disease activity and Indian version of the HAQ-DI was used for the measurement of functional disability among the patients.

SF 36 is a disease-independent tool used to assess health outcomes among patients suffering from various chronic diseases like RA and has been extensively used in several countries including India. It captures 8 different health concepts viz. physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health (GH) perceptions. In SF-36 analysis, the raw scores are converted into transformed score on a 0–100 range for 8 subscales wherein the high score defines a more favorable health state or a better quality of life.[11],[12],[13]

The Stanford Health Assessment Questionnaire is a popular instruments used globally for assessing the patient's level of functional ability in many disease areas, including RA. The current study utilized the Indian version of Health Assessment Questionnaire Disability Index, which has shown to have a very good sensitivity, test-retest reliability and construct validity. It consists of total 12 questions relevant to the Indian population and the total scores obtained divided by 12 gave the disability Index (range 0–3) with the higher score reflecting the greater level of disability.[14],[15]

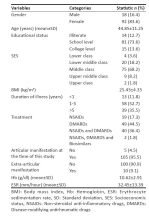
The DAS28 was utilized to assess the RA disease activity. It is a simple and widely used instrument for monitoring of disease activity in daily clinical practice consisted of measurement of a 28 tender joint count, a 28 swollen joint count, erythrocyte sedimentation rate or C-reactive protein, and a GH assessment on a visual analog scale. The overall range of the scores for DAS28 is 0–9.4. The level of RA disease activity can be interpreted as low if a DAS28 score is ≤3.2, a moderate disease activity if the score is between 3.2 and ≤5.1 and high disease activity for score >5.1. A score <2.6 corresponds with being in remission according to the American Rheumatism Association criteria.[16],[17]

Statistical methods

We analyzed the data using R Programming. The SES of the patient was calculated using the modified BG Prasad's classification and anemia status was determined according to the cutoff values recommended by the World Health Organization. Anemia was considered for males with hemoglobin <13 g/dL and females <12 g/dL.[18],[19] Cause and effect relationship of observed variables such as socio-demographic variables, disability index, DAS28 and HRQOL of RA patients is assessed by multiple linear regression models. The regression model included the various domains of HRQOL as a dependent variable and DAS28, duration of illness, HAQ-DI and SES as independent variables. Invariance and multicollinearity of the endogenous variables and structural relationship of latent variables are dealt with the aid of SEM. The latent variable “GenPHYS” was composed of four subscales of the SF-36 which includes physical functioning, role functioning/physical, bodily pain and role functioning/emotional whereas the latent variable “GenMENT” was composed of the subscales consisting of GH, social functioning, emotional wellbeing and energy/fatigue.[20],[21] HAQ-DI, DAS28, socio-demographic and clinical characteristics of the patients were selected as manifest variables. The relationship between manifest variables and latent variables were assessed using SEM.

Results

Of the 110 patients, 92 (83.6%) were female. The mean age of the patients was 44.85 ± 11.25 years. The majority 81 (73.6%) had completed their education up to school level (higher secondary education). As per BG Prasad classification 75 (68.2%) belonged to the middle class and 2 (1.8%) were belonged to an upper class. The mean body mass index scores of the patients was 25.43 (±4.35) and around 56 (51%) were overweight/obese. The majority of patients were suffering from RA for a period of 1–5 years 58 (52.7%) and more than 5 years 39 (35.5%). The majority of the patients 105 (95.5%) had articular manifestation, 10 (9.1%) of the patients had extra articular manifestation and 74 (67.3%) were anemic [Table 1].



Variables	Categories	Statistic n (%)
Gender	Male	18 (16.4)
	Female	92 (83.6)
Age (years) (mean±SD)		44.85±11.25
Educational status	Illiterate	14 (12.7)
	School level	81 (73.6)
	College level	15 (13.6)
SES	Lower class	2 (1.8)
	Lower middle class	29 (26.2)
	Middle class	75 (68.2)
	Upper middle class	3 (2.7)
	Upper class	1 (1.0)
BMI (kg/m²)		25.43±4.35
Duration of illness (years)	<1	15 (13.8)
	1–5	58 (52.7)
	>5	39 (35.5)
Treatment	NSAIDs	10 (17.2)
	DMARDs	40 (44.5)
	NSAIDs and DMARDs	40 (36.4)
	NSAIDs, DMARDS and Biosimilars	2 (1.8)
Articular manifestation at the time of this study	No	5 (4.5)
	Yes	105 (95.5)
Extra-articular manifestation	No	100 (90.9)
	Yes	10 (9.1)
Hb (g/dl) (mean±SD)		10.82±1.91
ESR (mm/hour) (mean±SD)		32.45±13.96

BMI: Body mass index, Hb: Hemoglobin, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, SES: Socioeconomic status, NSAIDs: Non-steroidal anti-inflammatory drugs, DMARDs: Disease-modifying antirheumatic drugs

Table 1: Sociodemographic and clinical characteristics of rheumatoid arthritis patients

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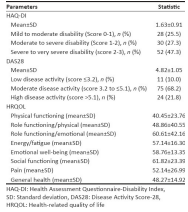
[Table 2] shows the HRQOL-SF36, DAS28 and HAQ-DI scores of the patients. Quality of health indicators such as social functioning, role functioning/emotional, emotional well-being, energy/fatigue and pain had the higher scores like 61.82 (±23.39), 60.61 (±42.16), 58.76 (±13.35), 57.14 (±16.30) and 52.14 (±26.99) respectively when compared with the other subscales of SF 36 like role functioning/physical 48.86 (±40.55), GH 48.27 (±14.92) and physical functioning 40.45 (±23.76) which had the lower scores. The mean DAS28 score was 4.82 (±1.05) and the majority of them 75 (68.2%) were having moderate disease activity. The mean HAQ-DI score was 1.63 (±0.91) and a total of 52 (47.3%) were having severe disabilities.



Parameters	Statistic
HAQ-DI	
Mean±SD	1.63±0.91
Mild to moderate disability (Score 0-1), *n* (%)	28 (25.5)
Moderate to severe disability (Score 1-2), *n* (%)	30 (27.3)
Severe to very severe disability (score 2-3), *n* (%)	52 (47.3)
DAS28	
Mean±SD	4.82±1.05
Low disease activity (score ≤3.2), *n* (%)	11 (10.0)
Moderate disease activity (score 3.2 to ≤5.1), *n* (%)	75 (68.2)
High disease activity (score >5.1), *n* (%)	24 (21.8)
HRQOL	
Physical functioning (mean±SD)	40.45±23.76
Role functioning/physical (mean±SD)	48.86±40.55
Role functioning/emotional (mean±SD)	60.61±42.16
Energy/fatigue (mean±SD)	57.14±16.30
Emotional well-being (mean±SD)	58.76±13.35
Social functioning (mean±SD)	61.82±23.39
Pain (mean±SD)	52.14±26.99
General health (mean±SD)	48.27±14.92

HAQ-DI: Health Assessment Questionnaire-Disability Index, SD: Standard deviation, DAS28: Disease Activity Score-28, HRQOL: Health-related quality of life

Table 2: Mean scores of Health Assessment Questionnaire-Disability Index, Disease Activity Score-28 and health-related quality of life in rheumatoid arthritis patients

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[Table 3] shows the multiple linear models of HRQOL of RA patients. The model specified that age and gender are the

least important independent variables and hence excluded from the model. Physical functioning of the RA patients was significantly associated with duration of illness (1–5 years-β = −16.27; *P* = 0.001, >5 years -β = −28.05; *P* = 0.001), DAS28 (β = −12.68; *P* = 0.000), HAQ-DI (β = −3.66; *P* = 0.000) scores.

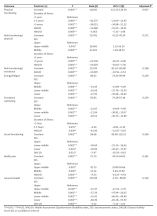

Table 3: Impact of sociodemographic variables, Health Assessment Questionnaire-Disability Index and Disease Activity Score-28 on the Health-related quality of life using multiple linear models

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Role functioning/physical of the RA patients was associated with SES, duration of illness, and HAQ-DI. More than 5 years of duration of illness was negatively associated with role functioning/physical (β = −21.53; *P* = 0.005). Similarly, upper middle (β = 28.69; *P* = 0.041), and middle class status (β = 22.82; *P* = 0.005), were positively associated with role functioning/physical.

Additionally, high DAS28 scores were significant predictors of several HRQOL domains like role functioning/emotional (β = −12.04; *P* = 0.002), social functioning (β = −5.47; *P* = 0.021), and GH (β = −3.22; *P* = 0.002), whereas high HAQ-DI scores were significantly associated with emotional wellbeing (β = −8.32; *P* = 0.039), and bodily pain (β = −9.33; *P* = 0.001).

Lower SES was significantly associated with the reduced scores of energy/fatigue (β = −27.95; *P* = 0.002), emotional well-being (β = −26.52; *P* = 0.001), social functioning (β = −20.99; *P* = 0.041) and GH (β = −68.39; *P* = 0.001), whereas duration of illness was found to be associated with reduced scores in emotional well-being (β = −4.36; *P* = 0.055).

[Table 4] includes two structural equation models, evaluating the relationship between the various factors and HRQOL. Model 1 has four manifest variables such as HAQ-DI, DAS28, SES and Duration of illness and two latent variables such as GenPHYS and GenMENT. These subscales were significantly associated with the latent variables in both the models.

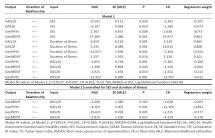

Table 4: Estimated coefficients from structural equation modeling for health related quality of life among rheumatoid arthritis patient

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In the model 1, SES was significantly associated with HAQ-DI (*P* = 0.026) and DAS28 (*P* = 0.020) as well as with GenPHYS (*P* = 0.008) and GenMENT (*P* = 0.001). Similarly, duration of illness was also associated with HAQ-DI and DAS28, GenPHYS and GenMENT (*P* = 0.001, 0.001, 0.001, 0.024 respectively).

HAQ-DI was significantly associated with GenPHYS and GenMENT (*P*= 0.001, 0.043) and DAS28 was also found to be associated with GenPHYS and GenMENT (*P* = 0.001, 0.014). The model fit indices of model 1 (χ^2 = 170.07: *P* = 0.001; Comparative Fit Index (CFI) = 0.853, Tucker-Lewis index (TLI): 0.789; Root Mean Square Error of Approximation (RMSEA) = 0.057) reveal that the model 1 was reasonably fit [Figure 1].

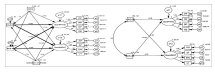

Figure 1: Model 1: Structural equation models of the relationship between HAQ DI, DAS28, and HRQOL in RA Patients. Circles represent latent variables (GenPHYS and GenMENT) and squares represent observed variables (SF 36 scales). Model 2: Structural equation models of the relationship between HAQ DI, DAS28, and HRQOL in RA Patients after controlling for SES and Duration of illness. PF: Physical functioning, RP: Role Physical, BP- Bodily Pain, RE Role emotional, GH: General health, SF: Social functioning, EW: Emotional well being, VT: Vitality, SES: Socioeconomic status, HAQ DI: Health Assessment Questionnaire Disability Index, HRQOL: Health related quality of life, RA: Rheumatoid arthritis

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Model 2 is the nested model of the model 1 in which we controlled the effect of SES and duration of illness which were considered as confounding variables. It is observed that HAQ-DI is a significant predictor of GenPHYS (*P* = 0.001) whereas DAS28 is a significant predictor of GenPHYS as well as GenMENT (*P* = 0.001, 0.025). Similarly HAQ–DI and DAS28 were covariance with each other (*r* = 0.54,*P*= 0.039).

The model fit indices of model 2 (χ^2 = 104.14: *P* = 0.001; CFI = 0.869; TLI =0.816 RMSEA = 0.044) reveal that the model 2 was a better fit [Figure 1].

Therefore, HAQ-DI and DAS28 predict the GenPHYS whereas DAS28 predict GenMENT irrespective of SES and duration of illness.

Discussion

In our study, we obtained lower scores in the domain of role functioning/physical, GH and physical functioning as compared with other subscale of the SF 36. This is similar to the findings of the other studies which reported the physical domain as a most affected domain of HRQOL.[4],[12] A systematic review and meta-analysis done by Matcham *et al*., showed that RA negatively impacts HRQOL and the impact is more severe on physical HRQOL domains as compared

with mental well-being[13] A strong social support, especially from the family members may be attributed to the higher scores of social functioning and emotional wellbeing in Indian patients with RA.

We observed moderate disease activity among the majority of the patients (68.2%) and almost half of them (47.3%) presented with a severe functional disability. The intensity of disease activity observed among our patient is lesser as compared with the other Indian studies in which the assessment was done at the initial presentation and this reduction can be attributed to the impact of their treatment over a period of time.[7],[22]

We performed the multiple linear regression analyses to evaluate the impact of various socio-demographic variables, functional disability and disease activity on the HRQOL. High HAQ-DI scores were significant predictors of several HRQOL domains like physical functioning, role functioning/physical and bodily pain, whereas high DAS28 scores were significantly associated with physical functioning, role functioning/emotional, social functioning and GH. Socio-economic status was found to be directly associated with all domains of HRQOL except physical functioning with lower classes reflecting the poorer quality of life among the patients.

In this study, we constructed models to exhibit the relationship between several distinct variables and the domains of HRQOL among patients with RA. Most of the authors have used the correlation analysis for evaluating the various factors affecting HRQOL of RA patient.[23],[24] To our knowledge, this study is first of its kind which focuses on establishing the relationships among these variables using a SEM among south Indian patients suffering from RA. SEM is the better tool for analyzing the latent variables. In addition, through SEM analysis, we can test and evaluate multivariate causal relationships. Through this approach we found SES and duration of illness as well as DAS28 and HAQ-DI are associated with HRQOL. While components of SES (income, education, etc.) act as potential confounders, few studies have investigated and proved the causal effect of SES on HRQOL and its role in disease related outcome should be viewed carefully.[25] People belonging to lower socio-economic status confront several barriers, including availability; accessibility and affordability to health care services leading to detrimental consequences in the long run, which often are reflected in poor self-reported outcomes like disability, quality of life and disease activity indices. Similarly, longer duration of illness was found to be negatively associated with the domains of physical and emotional well being. These findings are similar to the findings of other studies in India as well as other countries.[23],[24],[25]

We obtained an inverse relationship between HAQ-DI and DAS28 with HRQOL with a greater level of disability and high disease activity leading to lower scores in GenPHYS and GenMENT resulting in poor quality of life. Several studies have shown the strong correlation between high disease activity and disability with a physical component, and mental components of HRQOL. Although we have adopted a different methodology of analysis, our finding reaffirms the earlier findings. After controlling the effect of SES and duration of illness the association between DAS28 and GenPHYS and GenMENT persists whereas HAQ-DI found to have no impact on the mental component of HRQOL. In spite of the limitation of mobility and activities, the interplay of variety of factors like social support, coping strategies and disease acceptance plays an important role in psychosocial adjustment among individuals, enabling them to adapt to the demands of the chronically ill disease and disabilities leading to better psychological well-being.[26] In the present study, we obtained better scores in the domain of social functioning, however to substantiate the optimal social support, we need further exploration using a multidimensional measure of social support among RA Patients to understand its effect on the psychological wellbeing of the patients.

Limitations

The results of the study should be viewed carefully as we sampled the patients from a single hospital with relatively small sample size, which limits the generalisability of its findings to a broader population in the community. Similarly, no causal relationship can be ascertained between various factors and HRQOL by virtue of the observational nature of the study. Further exploratory studies are required to evaluate the factors like concomitant nutritional deficiency, community acquired infections, lower educational status, which are inextricably linked with lower SES.

Conclusions

The substantial impact of RA was observed in both physical and mental domains of HRQOL. The findings of this study are helpful in gaining an insight into the various factors and its inter-relationship using a structural equation model. The level of disability was having an impact on physical health, whereas disease activity was inversely associated with physical and mental health domains of HRQOL after controlling the effect of SES and duration of disease. To improve the overall health of the patient, it is crucial to assess patients and intervene appropriately through a multidisciplinary approach that will improve the long term health of the patients.

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Conflict of interest

There are no conflicts of interest.

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Figures

[Figure 1]

Tables

[Table 1], [Table 2], [Table 3], [Table 4]

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ORIGINAL ARTICLE PEER-REVIEWED

The Prevalence of Reproductive Tract Infections Based on the Syndromic Management Approach Among Ever-Married Rural Women in Kancheepuram District, Tamil Nadu: A Community-Based Cross-Sectional Study

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Abstract

Introduction

Reproductive tract infections (RTIs) are endemic among developing countries and common among females specifically in the reproductive age group. The sequelae of this lead to infertility. The main reason behind the high prevalence was found to be the lack of awareness about the disease and the stigma toward the disease.

Aims and objectives

This study aims to assess the prevalence of reproductive tract infection based on the syndromic management approach among ever-married rural women in the reproductive age group in the Kancheepuram District.

Methodology

This community-based cross-sectional study was conducted in the rural field practice area of Chettinad Hospital and Research Institute during the period from March 2016 to May 2017. The sample size taken was 330, and the sample size was arrived at by multistage random sampling and population proportion to size. Data were collected using a standardized questionnaire of District Level Household Survey 4 (DLHS-4) on RTI/sexually transmitted infections (STIs). Data were then entered in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and analyzed using SPSS version 21 (IBM Corp., Armonk, NY, USA), and results were interpreted.

Results

The prevalence of RTI was found to be 50.3%, with the majority (61.3%) of women in the age group of 28-37 years, 52.85% among females living with spouses, and 57.9% from the Hindu community. The prevalence was high among the lower-middle-class and nuclear families. The commonest symptom is vulval itching with 74.09%, and the least is boils with 0.9%. A significant association was noted between RTI and menstrual hygiene practices and socioeconomic status ($p < 0.05$).

Conclusion

The prevalence was high among rural females, and the main reason behind it was the stigma and the lack of awareness. Health education using various sources should be provided to get rid of these issues.

Introduction

Reproductive tract infection (RTI) is the infection of the reproductive tract; it is of three types: sexually transmitted infection (STI) such as chlamydia, gonorrhea, chancroid, and human immunodeficiency virus; endogenous infection due to the overgrowth of the normal flora of the reproductive tract; and iatrogenic infection, mainly due to improper procedures such as unsafe abortion and unhygienic delivery practices [1]. The WHO estimates that 80%-90% of the global burden lies in low-middle-income countries (LMICs) [2]. Although reproductive tract infection involves both men and women, it is most common among women, especially in the reproductive age group and specifically the ever-married women. The infection accounts for about 33% in females and 12.3% in males [3]. Every year, thousands of women expire due to or as the sequel of reproductive tract infection [1].

Globally, the prevalence of morbidity among females due to reproductive tract infection accounts for 22%, with the highest prevalence in South Asia and Sub-Saharan Africa with 150 million cases out of 340 million cases [4]. Curable infections such as bacterial vaginosis, gonorrhea, chlamydia, lymphogranuloma venereum, syphilis, trichomoniasis, and chancroid are common compared to incurable infections caused by the human papillomavirus, herpes simplex virus, and human immunodeficiency virus. In India, the annual incidence of reproductive tract infection and sexually transmitted diseases is projected as 5% or approximately 40 million every year [5]. According to the National Family Health Survey 4 report, 89.5% of rural women of the reproductive age group follow good menstrual hygiene, especially the age group of 15-24 years, among which only 15.6% were aware of reproductive tract infection and their spread [6]. The District Level Household Survey 4 (DLHS-4) conducted during 2012-2013 reported that the awareness about reproductive tract infection among the rural population of Tamil Nadu is 8%, and the awareness about the symptoms is 55.7% [7].

The most common presenting complaint of reproductive infection is vaginal discharge, the leading cause of gynecological morbidity [8]. Keeping in mind the complications and sequelae, the prevention, control, and management of reproductive tract infection are given high precedence in national programs such as Reproductive and Child Health II and National AIDS Control Program (NACP-IV) [9]. The key plan of the Reproductive and Child Health II and National AIDS Control Program is the execution of the syndromic management [9]. The syndromic management of reproductive tract infections/sexually transmitted infections is based on the symptoms and signs that are associated with the infection. The main objective of this approach is to identify and treat the syndromes with the blended therapy that covers the contributing organisms. This system is vastly sensitive, and the treatment is also given at the primary care level. The easy flow diagrams in this guideline help health workers in the early detection and treatment of the disease using laboratory analysis. The core drawback of the syndromic management approach is that 87% of the fund is spent on overtreatment [10]. The use of contraceptives also plays a vital role; users of intrauterine contraceptive devices (IUCDs) have a higher risk of developing infection compared with users of barrier contraceptives [11], and the control of reproductive tract infection is a crucial health priority in several countries [12]. Overcrowding also leads to the high prevalence of reproductive tract infections [13].

The Ministry of Health and Family Welfare, Government of India, decided to start the process of conducting DLHS-4 during the year 2012-2013. The questionnaires enclosing details about reproductive tract infection were considered for the study [7].

With this as the backdrop and with women from rural areas themselves being a high-risk factor for reproductive tract infection, this study mainly focused on estimating the prevalence of reproductive tract infection using the syndromic management approach among rural women in the reproductive age group, i.e., 18-49 years, in Kancheepuram District, Tamil Nadu.

Materials & Methods

Study design, period, and area

This study is a community-based cross-sectional study conducted for a period of 14 months from March 2016 to May 2017 in the field practice area of Chettinad Hospital and Research Institute.

Study population

The total population of villages in the field practice area is 39,545, among which 20,480 are males and 19,065 are female. From this female population, those who are less than 18 years old and more than 49 years old (N=14,003) were excluded, and 5,062 females under the reproductive age group were listed; samples are selected for the study.

Inclusion criteria

Ever-married females in the reproductive age group were included.

Exclusion criteria

Antenatal females, postnatal mothers, postmenopausal women, and women with terminal illnesses were excluded from the study.

Sample size

With 24% as average prevalence [14-16], 95% confidence interval, and 5% absolute error, the sample size calculated using the formula $4pq/d^2$ was 292, and accounting for 15% nonresponse rate, the sample size obtained was 330.

Sampling technique

A multistage random sampling technique was used to select villages, and each village is considered a cluster. The population proportion to size method was used in selecting the samples from each cluster.

Study tool

A structured questionnaire containing sociodemographic factors such as age, educational status, qualification, socioeconomic status, family profile, environmental history, and menstrual and obstetric history; a standard questionnaire consisting of menstrual hygiene and personal hygiene practices; and questions eliciting symptoms of reproductive tract infection, such as vaginal discharge, vulval itching, abdominal pain, low backache, dyspareunia, and post-coital spotting, along with questions describing their pattern of treatment, were used as a study tool.

Data collection

The questionnaires were explained to ever-married females in the reproductive age group and filled out using the interview method.

Statistical analysis

The data collected were entered in Microsoft Excel (Microsoft Corp., Redmond, WA, USA), and statistical analysis was done using the SPSS software version 21 (IBM Corp., Armonk, NY, USA) [17]. The Chi-square test was applied for significance. P-value < 0.05 was considered significant.

Ethical consideration

The study was conducted after obtaining ethical approval from the institutional ethical committee of Chettinad Hospital and Research Institute with IRB number 23/ IHEC/ 3-16. Informed written consent was obtained from the participants.

Results

The prevalence of reproductive tract infection using the syndromic management approach among the rural women of the reproductive age group in Kancheepuram District was 50.3%. Table *1* shows the distribution of the study participants with the reproductive tract infection based on sociodemographic factors. The prevalence of this infection was high among the young adult females who are 18-27 years old (61.3%). According to literacy status, the prevalence of reproductive tract infection was comparatively found to be high in the graduates (48.2%), and it also increases with the decreasing level of socioeconomic status and higher in the lower-middle class (52.9%). The prevalence of infection was high among females living with spouses (52.8%) and living in nuclear families (53.6%).

Variables	Total (N=330)	RTI (N=166)
Age group		
18–27	75	46 (61.3%)
28–37	156	74 (47.3%)
38–49	99	46 (46.4%)
Marital status		
Living with husband	299	158 (52.8%)
Widow	18	5 (27.2%)
Divorce	13	3 (23%)
Religion		
Hindu	233	135 (57.9%)
Christian	66	27 (40.9%)

Muslim	31	4 (12.9%)
Educational status		
Primary	56	23 (41%)
Middle school	32	26 (81.2%)
High school	79	35 (44.3%)
Higher secondary	54	25 (46.2%)
Graduate	58	28 (48.2%)
Illiterate	51	19 (37.2%)
Socioeconomic class		
Upper	9	2 (22.2%)
Upper middle	49	20 (40.8%)
Lower middle	134	71 (52.9%)
Upper lower	103	51 (49.5%)
Lower	35	16 (45.7%)
Type of family		
Nuclear	194	104 (53.6%)
Joint	81	40 (49.3%)
Three generation	55	22 (40%)

Table 1: Distribution of RTI among the study participants according to selected sociodemographic characteristics

The prevalence of infection was high (80%) among females who had poor personal hygiene and menstrual hygiene practices (69.2%). Table *2* shows the prevalence of reproductive tract infection based on personal hygiene practices such as sanitary practice and menstrual hygiene followed.

Hygiene practices	Total (N=330)	RTI (N=166)
Sanitary facility		
Good	320	158 (49.3%)
Poor	10	8 (80%)
Menstrual hygiene		
Sanitary napkin	242	106 (43.8%)
Cloth	78	54 (69.2%)
Locally prepared napkin	10	6 (60%)

Table 2: Distribution of RTI among the study participants according to hygiene practices

The most common symptom presented by the study participants was vulval itching with 74.09%, while the least common complaint was boils with 1.8%. Table *3* describes the prevalence of the various symptoms of reproductive tract infection among the study participants.

Symptoms of reproductive tract infection	Frequency (N=166)	Percentage (%)
Vulval itching	123	74.09
Low backache	120	72.28
Vaginal discharge	105	63.25
Dyspareunia	48	28.91

Lower abdominal pain	36	21.68
Dysmenorrhea	7	04.21
Post-coital bleeding	3	01.80
Boils	3	01.80

Table 3. Prevalence of the symptoms of reproductive tract infection

A significant association was noted among the age factor and the symptoms of vulval itching and dyspareunia, while educational status had an association significant only with dyspareunia, as an increasing level of education decreases the stigma about the disease. A significant association was noted between socioeconomic status and vulval itching, low backache, and dyspareunia. Table *4* shows the association between the various demographic factors and the various symptoms of reproductive tract infection.

Demographic characteristics	**Reproductive tract infection symptoms**						
	Vulval itching (N (%))	Low backache (N (%))	Vaginal discharge (N (%))	Dyspareunia (N (%))	Dysmenorrhea (N (%))	Lower abdominal pain (N (%))	Post coita blee (N (%
Age (years)							
18–27	36 (29.3)	33 (27.5)	31 (29.5)	15 (31.3)	9 (25)	1 (14.3)	1 (33
28–37	58 (47.2)	55 (45.8)	49 (46.7)	27 (56.3)	16 (44.4)	6 (85.7)	2 (6
38–49	29 (23.6)	32 (26.7)	25 (23.8)	61 (12.5)	11 (30.6)	0	0
Chi-square	6.338	2.671	5.109	8.487	0.164	4.605	1.29
P-value	0.041*	0.263	0.078	0.014*	0.921	0.100	0.52
Education							
Primary	18 (14.6)	19 (15.8)	16 (15.2)	3 (6.3)	4 (11.1)	1 (14.3)	0
Middle school	18 (14.6)	17 (14.2)	11 (10.5)	12 (25)	5 (13.9)	0	0
High school	32 (26)	22 (18.3)	27 (25.7)	5 (10.4)	5 (13.9)	1 (14.3)	0
Higher secondary	14 (11.4)	21 (17.5)	18 (17.1)	14 (29.2)	10 (27.8)	2 (28.6)	1 (33
Graduate	25 (20.3)	19 (15.8)	18 (17.1)	11 (22.9)	5 (13.4)	2 (28.6)	1 (33
Illiterate	16 (13)	22 (18.3)	15 (14.3)	3 (6.3)	0	1 (14.3)	1 (33
Chi-square	10.489	7.990	0.781	31.277	17.201	2.152	3.119
P-value	0.063	0.157	0.978	0.000*	0.206	0.828	0.68
Socioeconomic status							
Upper class	2 (1.6)	3 (2.5)	2 (1.9)	1 (2.1)	1 (2.8)	0	0
Upper middle	10 (8.1)	12 (10)	15 (14.3)	11 (22.9)	8 (22.2)	0	0
Lower middle	51 (41.5)	70 (58.3)	45 (42.9)	10 (20.8)	20 (55.6)	2 (28.6)	0
Upper lower	46 (37.4)	27 (22.5)	37 (35.2)	15 (31.3)	6 (16.7)	4 (57.1)	2 (6
Lower	14 (11.4)	8 (6.7)	6 (5.7)	11 (22.9)	1 (2.8)	1 (14.3)	1 (33
Chi-square	9.384	24.960	4.881	15.982	8.778	3.144	4.55

P-value	0.050*	0.000*	0.300	0.0003*	0.067	0.534	0.34
Marital status							
Living with spouse	107 (87)	121 (98.8)	93 (88.6)	48 (97.9)	36 (100)	7 (100)	3 (10
Widow	9 (7.3)	5 (4.2)	7 (6.7)	0	0	0	0
Divorce	6 (4.9)	2 (1.7)	4 (3.8)	1 (2.1)	0	0	0
Chi-square	3.607	4.988	2.615	2.022	4.339	0.768	0.32
P-value	0.307	0.173	0.455	0.568	0.227	0.857	0.95

Table 4: Association between symptoms of reproductive tract infection and its determinants
*Significant at a p-value of 0.05

No association was noted between personal hygiene practices and symptoms of reproductive tract infection, while menstrual hygiene practices had a significant association with vaginal discharge and dysmenorrhea. Table *5* shows the association between hygiene practices such as sanitation and menstrual hygiene and various symptoms of reproductive tract infection.

Hygiene practices	**Reproductive tract infection symptoms**						
	Vulval itching (N (%))	Low backache (N (%))	Vaginal discharge (N (%))	Dyspareunia (N (%))	Dysmenorrhea (N (%))	Lower abdominal pain (N (%))	Post-coital bleeding (N (%))
Sanitary facility							
Good	121 (98.4)	119 (99.2)	103 (98.1)	48 (100)	35 (97.2)	7 (100)	3 (100)
Poor	2 (1.6)	1 (0.8)	2 (1.9)	0	1 (2.8)	0	0
Chi-square	1.316	3.907	.664	1.755	0.009	0.223	0.095
P-value	0.332	0.100	0.512	0.368	1.000	1.000	1.000
Menstrual hygiene practices							
Sanitary napkin	97 (78.9)	92 (76.7)	99 (94.3)	37 (77.1)	35 (97.2)	7 (100)	3 (100)
Cloth	21 (17.1)	26 (21.7)	2 (1.9)	11 (22.9)	0	0	0
Locally prepared napkin	5 (4.1)	2 (1.7)	4 (3.8)	0	1 (2.8)	0	0
Chi-square	5.084	1.752	40.297	1.822	12.704	2.601	1.101
P-value	0.079	0.416	0.000*	0.402	0.002*	0.272	0.577

Table 5: Association between symptoms of reproductive tract infection and hygiene practices
*Significant at a p-value of 0.05

Discussion

The findings of our community-based study among ever-married females of the reproductive age group in the rural areas of Kancheepuram District indicated that more than half (50.3%) of them were suffering from either one of the symptoms of RTI. These symptoms were high among the age group of 18-27 years (61.3%), and it was also high among females who were living with

their husbands (52.8%) compared to widowed and divorced females. Symptoms were more among the Hindu community (57.9%), those with middle school standard (81.2%), and those with lower-middle-class socioeconomic status (52.9%). The commonest symptom was vulval itching (74.09%), which was high among the age group of 28-37 years; it was 41.5% in the lower-middle class, 76.2% among Hindu females, and 82% among females living with their partners. It was followed by low backache (72.28%), which is high among those who are 28-37 years old (45.8%), in the lower-middle class (58.3%), Hindu (76.7%), and living with spouses (93.3%). Vaginal discharge was at 63.25%, which was high among the age group of 28-37 years (46.7%), females in the lower-middle class (42.9%), those living with spouses (88.6%), and those living in nuclear families (64.8%).

A similar study conducted in Surendranagar District indicated a prevalence rate of 56.9%, and the prevalence was common among the low socioeconomic group. The commonest symptom reported was vaginal discharge with 26.3% [13]. The prevalence of RTI was estimated to be 51.9% in a study conducted in Sirmaur; the frequently occurring symptom was vaginal discharge with 51.9%, and the age group affected was 25-34 years, with a prevalence of 63.6%. There was an increasing trend of prevalence among the illiterate, with a prevalence of 72%, with a frequent complaint of vaginal discharge (51.9%) [17]. A study conducted in Raichur reported a prevalence rate of 58.9%, the most common symptom being vaginal discharge (27%). The prevalence was high among the mid-reproductive age group (25-34 years), and socioeconomic status plays a major role in the prevalence of RTI [18]. The study that was conducted in the Chennai basis areas showed a prevalence of reproductive tract infection of 45.5%, with the common symptom being vaginal discharge (35%) [19]. The epidemiological study conducted in the Bundelkhand region of Uttar Pradesh reported a prevalence of infection of 44.6%, with the common presenting symptom being vaginal discharge (74.2%), followed by vulval itching (35.6%). The prevalence was high among the age group of 25-29 years and those with low socioeconomic status, and there is also an association between literature status and the prevalence of infection. The prevalence was high among cloth users with 43.6% and those using sanitary pads with 31.3% [20]. A community-based study on reproductive tract infection in a district of West Bengal indicated a very low prevalence of 9.85%. The presenting symptom vaginal discharge falls under the high category, with a prevalence of 45%. The prevalence among the age group of 24-29 years was high with 11.39%. Females who reported the symptoms had low socioeconomic status (53.5%), and it is 6.89% among those with higher standards [21]. A cross-sectional study of a rural community in Hooghly District reported the prevalence of reproductive tract infection to be 13.7%. Vaginal discharge is the most common symptom (7.5%) [9].

Limitation of the study

The prevalence of the RTI was estimated only based on the symptoms of the infection presented by the study participants; clinical examination and laboratory investigations were not conducted to confirm any infections.

Conclusions

In conclusion, RTI was common among females of the reproductive age group in the rural community with high prevalence such that more than half of the study population had either one of the symptoms of reproductive tract infection, and the association was also found to be significant. This is mainly due to several reasons, such as lack of awareness about the symptom of the disease, stigma in using terms such as white discharge, vulval itching, and pain during sexual contact that describe the symptoms associated with the disease, and poor menstrual hygiene and personal hygiene practices.

To overcome all these reasons, females of the reproductive age group in rural areas should be provided with regular health education regarding the symptoms of RTI and should also be motivated to seek proper management for that particular complaint. Health education in the area of menstrual hygiene and personal hygiene should be provided not only to females of the reproductive age group but also to females of the adolescent age group, which can help in reducing the prevalence of reproductive tract infection. Our study also suggests that health education should be mainly imparted to females of low socio-economic class and early adults to overcome the symptoms of RTI, and this might be an immediately feasible method to decrease the burden of the disease in the community. Health education on personal and menstrual hygiene practices using the various study material (IEC) is recommended to decrease the burden of the problem, and it is also most important to involve adolescent females, those both at high school and college, in health education for the betterment of the situation.

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Original Article

Opioid-free anaesthesia for laparoscopic surgeries - A prospective non-randomised study in a tertiary care hospital

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ABSTRACT

Background and Aims: Opioids have nowadays become superfluous because of their adverse effects involving post-operative recovery of the patients. So, we aimed at comparing opioid-free anaesthesia with opioid-based technique for post-operative pain relief in laparoscopic surgeries. The primary objective was to assess the pain scores in the post-operative period using visual analogue scale (VAS) for 24 h, and the secondary objective was to compare intraoperative haemodynamic parameters, duration of postoperative analgesia and total analgesics consumed in the first 24 h. **Methods:** This study was conducted in 60 patients aged between 20 and 70 years, belonging to the American Society of Anesthesiologists physical class I and II posted for laparoscopic surgeries. Anaesthetic doses of lidocaine, magnesium and paracetamol in combination with fascial plane block for post-operative pain relief were given for 30 patients, and the other 30 patients received the conventional opioid-based anaesthesia. Mann–Whitney test was used for VAS scores, and Friedman test was used for repeated measures comparison. **Results:** VAS scores were higher in the conventional group as compared to the opioid-free group at 0, 2, 4, and 6 h during rest and at 0, 2, 4, 6, 24 h during movement and were statistically significant (*P*-value < 0.05). The duration of analgesia for the conventional group was 13.8 + 6.7 h, and for opioid-free anaesthesia was 6.7 + 2.2 hours. Intraoperative haemodynamic parameters did not show a statistically significant difference except for systolic blood pressure which was higher in the opioid-free group but was clinically insignificant. (*P*-value 0.013). **Conclusion:** Opioid-free anaesthesia along with erector spinae plane block provides better post-operative pain relief when compared to conventional opioid anaesthesia.

Key words: Block, magnesium, opioid, postoperative pain

INTRODUCTION

Though laparoscopic surgeries are considered relatively painless and are associated with early recovery and lesser duration of hospital stay, they can cause severe pain, especially in the first 4 h of the immediate post-operative period.[1] This may be attributed to the peritoneal irritation caused by the carbon dioxide insufflation pressures, bowel handling by the surgeons or irritation caused by the residual or retained blood. Opioids have been the main mode of analgesia in the perioperative period and are associated with significant side effects such as dizziness, sedation, nausea, constipation, vomiting, physical dependence, muscle rigidity, tolerance, respiratory depression and addiction.[2] The prevalence of opioid use in India is around 0.7%, and it has twice the global prevalence of illicit consumption from drug abuse and dependence.[3] Acute surgical pain in

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the immediate post-operative period is a significant risk factor for the development of chronic pain and controlling it is a key factor for reducing the risk of chronic post-operative pain.[4] Anaesthesiologists play an important role in identifying at-risk patients for long-term opioid use and thereby reducing perioperative opioid administration and decreasing related side effects.[5] Though opioid-free regimens have been studied earlier, there is sparsity of literature incorporating regional anaesthesia and avoiding ketamine use in such regimens.[6] This study was planned to provide multimodal analgesia with drugs other than opioids such as lignocaine, magnesium along with fascial plane blocks for post-operative analgesia with an aim to reduce opioid requirement and its associated adverse effects. The main objective was to compare the post-operative pain scores using visual analogue scale (VAS) between the opioid-free anaesthesia and opioid-based technique.

METHODS

This prospective non-randomised study was conducted in a tertiary care hospital from September 2020 to April 2021 for a period of 8 months after getting Institutional Ethics Committee approval in accordance with the declaration of Helsinki. Each patient was given a form explaining the drugs used, fascial plane blocks performed and their postoperative analgesic effects, and informed consent was obtained. Patients aged between 20 and 70 years, with the American Society of Anesthesiologists physical status I and II posted for laparoscopic surgeries were included in the study. Participants having body mass index >35 kg/m^2, known allergy to local anaesthetic agents, or having liver and renal insufficiency were excluded. Conversion to open technique and continuation of post-operative ventilation were considered as dropouts. Laparoscopic surgeries performed were cholecystectomy, appendicectomy, and totally extraperitoneal inguinal hernia repair. A group size of 30 was calculated using power analysis based on a previous study report.[7] Convenience sampling was done, and the study included 60 patients out of which 30 patients were given opioid-sparing anaesthesia, and the rest 30 patients received the conventional opioid-based anaesthesia. The primary objective was to compare the pain scores in the post-operative period using VAS for 24 h, and the secondary objective was to compare intra-operative haemodynamic parameters, duration of postoperative analgesia (defined as the time from completion of erector spinae plane block (ESPB) post-induction till the first analgesic requirement as indicated by VAS >5) and total analgesics consumed in the first 24 h.

A routine pre-operative evaluation was done and on the arrival of the patients to the theatre complex, the intravenous (IV) cannula was checked for the flow and patency. Pre-loading was done using IV crystalloids 10 mL/kg. Pre-emptive analgesia was given using IV dexamethasone 8 mg and IV paracetamol 15 mg/kg. Baseline parameters such as heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), oxygen saturation, respiratory rate and end-tidal carbon dioxide monitoring were noted. After pre-oxygenation with 100% oxygen, anaesthesia was induced with IV propofol mg/kg, lignocaine 1.5 mg/kg (bolus dose) and succinlycholine 1.5 mg/kg. Endotracheal intubation was done, and cisatracurium 0.2 mg/kg was administered. Anaesthesia was maintained using nitrous oxide 0.5 L/min, oxygen 0.5 L/min, sevoflurane 1%, and cisatracurium was administered in incremental doses as needed.

During the maintenance phase, opioid-free anaesthesia group received lidocaine 1.5 mg/kg as infusion along with magnesium 2 g (bolus dose) as a slow intravenous injection. Analgesia was supplemented with ESPB post-induction under ultrasound guidance with the patient in lateral position. High-frequency linear probe "(sonosite - Fujifilm)" was used and positioned longitudinally at the level of the T6 vertebra in a parasagittal orientation, with the end of rhomboid muscle as the landmark.[8] Tip of the transverse process of the corresponding vertebra along with the underlying pleura was visualised, and the target was to open up the plane between the erector spinae muscle and the transverse process [Figure 1]. The

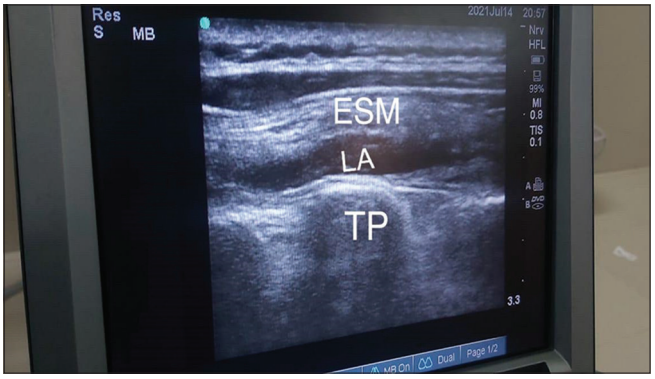

Figure 1: Image showing erector spinae plane with transducer placed in a parasagittal orientation and local anaesthetic is seen deposited underneath the erector spinae muscle. [ESM = Erector spinae muscle, LA = Local anaesthetic, TP = Transverse process]

tip of the stimuplex (B Braun) needle was advanced using in-plane technique in a craniocaudal direction to contact the transverse process. Hydro dissection was done to visualise needle position deep to erector spinae muscle. After confirmation, 30 mL of 0.25% bupivacaine was injected deep into the muscle bilaterally (total volume 60 mL).

Haemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were monitored just before induction and at 5, 10, 15, 30, 60 min after induction for all patients. Non-opioid analgesic, injection paracetamol 1 g, was given by the end of surgery intravenously.

In the conventional opioid-based anaesthesia group, a similar induction protocol was followed. Intraoperative rise in blood pressure was maintained with fentanyl boluses of 0.5 μg/kg. At the end of the surgery, all the patients received paracetamol 1 g and ondansetron 4 mg intravenously.

In both the groups, intra-abdominal pressure during pneumoperitoneum was maintained within 12–15 mm Hg. End-tidal carbon dioxide was maintained at less than 35 mmHg. Conventionally, four ports were made for all the laparoscopic surgeries with a 10 mm port at the level of the xiphoid process and the lowermost port at the level of the umbilicus (T6–T10).

After extubation, pain scores, vital signs and any adverse effects in the post-anaesthesia care unit were assessed in all patients. Follow up scores and monitoring were done at 0, 2, 4, 6, 12, 24 hours postoperatively and rescue non-opioid analgesic paracetamol 1 g was given if VAS score was >5 and for those complaining of persistent severe pain [VAS 8–10] limiting movement, opioid analgesic was given in the form of injection tramadol 50 mg. During the follow up period, the time for the first analgesic request and the total analgesic consumption was documented in the data collection proforma.

Data analysis was done using R programming 3.6.1 version (GNU GPL v2) and entered in Microsoft excel sheet. Descriptive statistics were calculated for all variables in which categorical variables were expressed as frequency, and numerical variables were expressed as mean ± standard deviation. Mann–Whitney test was used to compare the VAS score between both the groups. Friedman test was used for repeated measures comparison. A confidence interval of 95% was used in all statistical tests, and *P* value <0.05 was considered significant.

RESULTS

Sixty-eight patients were assessed for eligibility, and sixty patients were recruited. All of them completed the study and were included in the analysis. VAS score for pain comparison both during rest and movement was significantly higher in the conventional group at 0, 2, 4, 6, 12, 24 h postoperatively than in the opioid-free anaesthesia group [as shown in Tables 1 and 2]. The total duration of analgesia differed significantly among both the groups. Duration of analgesia achieved with opioid-free anaesthesia group was 13.8 ± 6.7 h which is significantly higher as compared to the conventional group (6.7 ± 2.2) h. There was no significant difference in the duration of surgery between the groups [Table 3]. In the opioid-free anaesthesia group, about 23% (n = 7) did not require any analgesics in the post-operative period for the first 24 h. The total postoperative consumption of analgesics differed between both the groups. About

Table 1: VAS score comparison at rest

Variables	Opioid-free anaesthesia (Median)	Conventional group (Median)	*P*
VAS 0 hour	2	4	0.000
VAS 2	2	4	0.000
VAS 4 h	2	4	0.000
VAS 6 h	2	4	0.000
VAS 12 h	1	2	0.177
VAS 24 h	0	1	0.606

**P* (< 0.05) = statistically significant. VAS=Visual Analogue Scale

Table 2: VAS score comparison during movement

Variables	Opioid-free anaesthesia) (Median)	Conventional group (Median)	*P*
VAS 0 h	3	5	0.001
VAS 2 h	3	5	0.002
VAS 4 h	3	5	0.000
VAS 6	2	3	0.077
VAS 12 h	2	2	0.744
VAS 24 h	2	2	0.036

**P* (<0.05) = statistically significant. VAS=Visual Analogue Scale

Table 3: Duration of analgesia and surgery using descriptive statistics

Variable	Opioid-free anaesthesia Mean±SD	Conventional group Mean±SD
Age (years)	43.87±10.51	42.26±12.56
Duration of surgery (h)	1.61±0.35	1.43±0.53
Duration of analgesia (h)	13.80±6.73	6.71±2.20

SD- standard deviation

67% (n = 20) required one dose of paracetamol (1 g) and 32% (n = 10) required one dose of paracetamol along with opioid (tramadol 50 mg) in view of severe pain as assessed by VAS (score > 5) in the conventional group, whereas 63% (n = 19) required one dose of paracetamol (1 g) and 13% (n = 4) required two doses of paracetamol (total 2 g) at an interval of 8 to 12 h in the opioid-free anaesthesia group [Table 4]. Clinically, haemodynamic parameters were comparable among the opioid-free anaesthesia group and the conventional group. Inferential statistics was applied, and the results showed that both groups did not show any significant difference in heart rate (0.72 bpm; 95% CI [-3.92 to 5.63], $P = 0.72$) and diastolic blood pressure (0.064 mmHg; 95% CI [-0.26 to 8.96], $P = 0.06$) but had a statistically significant decrease in systolic blood pressure in the conventional group (0.01 mm Hg; 95% CI [1.41 to 11.31], $P = 0.013$). However, the difference was clinically insignificant. Similarly, the difference in mean arterial pressure (MAP) (P = 0.01) was statistically significant [Table 5].

DISCUSSION

In the current study, lesser VAS scores were seen postoperatively in the opioid-free group. This can be attributed to the use of fascial plane block which is part of our routine care for laparoscopic surgeries and our opioid-sparing regimen which included lignocaine and magnesium. A randomised controlled trial (RCT) on 40 patients to evaluate the efficacy of ESPB on cholecystectomy, where both the groups received IV patient-controlled analgesia containing morphine showed that pain scores were 0 at 12 and 24 h compared to pain scores (0–1) at 12 and 24 h of the control group, and the difference was statistically significant.[8]

Additionally, in the current study, the greater difference in duration of analgesia (7 hours) among both the groups is ascribed to the ESPB and the volume used (60 mL) which emphasises its efficacy in post-operative pain relief. Also, ESPB was combined with systemic non-opioid analgesics such as lignocaine and magnesium infusions for desired results, and ketamine was avoided due to its adverse effects and impact on recovery such as emergence reactions, hallucinations, dissociative states, apnoea, and vivid dreams. This makes our study interesting and different from previous studies on opioid-free analgesia.

In the opioid-free anaesthesia group, total analgesic consumption was less, and none required opioid as rescue analgesia, whereas in the conventional opioid group, 10 patients required tramadol 50 mg secondary to paracetamol as they had a higher VAS score which limited movement. This proves to us that a multimodal analgesic approach will eliminate the need for opioids in the perioperative period.

ESPB is a recently described technique, by Forero *et al*.[9] for treating chronic thoracic neuropathic pain. Local anaesthetic injected in EPSB, diffuses along the thoracolumbar fascia and exerts its effects on the ventral and dorsal rami of the spinal nerve providing visceral and somatic analgesia.[10] A study conducted on open cardiac surgeries showed that continuous ESPB produced a significant decrease in morphine consumption, rapid patient mobilisation and reduced pain.[11] As this procedure is safe and easy to perform, several authors have expressed their opinion that it could be part of the multimodal analgesia for the 'enhanced recovery after surgery' programmes.[11]

A meta-analysis in 2014 evaluated the clinical consequences of intraoperative doses of opioid and revealed that high doses of opioids during surgery cause higher acute postoperative pain, leading to increased postoperative analgesic consumption and long-term analgesic use.[12] The capacity of opioids to increase the area of secondary hyperalgesia around the surgical wound has been highlighted in a few clinical studies. This is associated with two inter-related phenomena called as 'tolerance' and 'opioid-induced hyperalgesia' which are mostly observed with remifentanyl infusions.[13]

Table 4: Consumption of analgesics using frequency table

Variables	Opioid-free anaesthesia *n* (%)	Conventional group *n* (%)
No dose of analgesics	7 (23)	-
1 dose of paracetamol	19 (63)	20 (67)
2 doses of paracetamol	4 (13)	-
1 dose of paracetamol + tramadol	-	10 (32)

n- number

Table 5: Comparison of intraoperative haemodynamics

Variables	Opioid-free anaesthesia Mean±SD	Conventional group Mean±SD	*P*
SBP (mmHg)	117.33±9.89	110.97±9.44	0.013
DBP (mmHg)	79.83±8.75	75.48±9.25	0.064
HR (bpm)	73.47±8.00	72.61±10.43	0.722
MAP (mmHg)	92.53±8.10	87.22±7.76	0.011

**P* (< 0.05=statistically significant); SBP=systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate MAP=Mean arterial pressure, SD=standard deviation

Lidocaine, a prototype of amino-amides, is a weak base and short-acting local anaesthetic. At higher levels, side effects such as confusion, agitation, metallic taste, perioral numbness, dizziness, slurred speech, diplopia, tinnitus, muscular spasms, and seizures are being reported. Perioperative advantages of intravenous lignocaine include reduction in pain, nausea, opioid consumption, inflammation and early bowel function after surgery.[14] Analgesic effects of lignocaine are noted with levels lower than 5 μg/mL.

Additionally, it has anti-hyperalgesic and anticonvulsant properties.[15] Intraoperative lidocaine infusion reduces the requirement of inhalational agents, muscle relaxants, and reduces post-operative ileus. In the current study, repeat doses of muscle relaxants were not required throughout the surgery which provided an added advantage with respect to cost-effectiveness. A Cochrane review study which included 68 RCTs showed that continuous infusion of lidocaine did not show a significant difference in pain scores at 24 h verrsus the placebo group.[16] Also, the effects of IV lignocaine on anaesthetic requirement and intraoperative haemodynamics have been evaluated in numerous clinical trials. A double-blinded RCT showed no significant differences in MAP and heart rate before induction, during surgery and in the recovery but showed that mean end-tidal sevoflurane concentration was 48% lower in the lignocaine group.[17] In the current study, haemodynamic parameters remained almost stable in 80% of the patients in both the groups and in those who had intraoperative rises in blood pressure, diltiazem 5 mg was given as needed.

Also, magnesium, an N-methyl-aspartate receptor antagonist, exerts its analgesic effects by regulating calcium entry into the cells. It prevents central sensitisation and abolishes hypersensitivity in post-injury states.[18] Data have been published regarding the role of magnesium in reducing anaesthetic requirements and achieving controlled hypotension.[19]

In the current study, intraoperative use of magnesium sulphate ($MgSO_4$) was associated with better intraoperative haemodynamics and good post-operative analgesia with no obvious side effects. A meta-analysis of four RCTs on the analgesic effect of magnesium after laparoscopic cholecystectomy reported a substantial decrease in pain scores at an early stage (at 2 and 8 h) and reduction in analgesic consumption post-operatively.[20] Also, a systematic review of 11 RCTs showed that perioperative administration of $MgSO_4$ intravenously could reduce adverse effects such as vomiting, nausea, shivering and post-operative analgesic consumption.[21]

Several studies have been published regarding various regimens for opioid-free anaesthesia. An RCT showed that using propofol, dexmedetomidine and lignocaine infusions for laparoscopic cholecystectomy was associated with lower pain scores, reduced rescue analgesia consumption and was also described as an alternative to opioid, especially for patients at high risk for post-operative nausea and vomiting.[22] In the current study, none of the patients experienced significant adverse effects of opioids in the post-operative period like nausea, vomiting, respiratory depression and ileus. One-third of the patients had right shoulder tip pain in the recovery room post-surgery which is attributed to the effects of residual carbon dioxide.

There are a few limitations in this study. This study is limited by biases as randomisation was not done. Secondly, VAS >5 was taken as cut-off for pain management because higher VAS scores limit movement and cough thereby delaying ambulation and recovery. Hence, results with other studies may be dissimilar.

CONCLUSION

Integration of ESPB into intravenous opioid-free analgesic regimen using lignocaine and magnesium provides better postoperative pain relief with lower VAS scores, increased duration of analgesia and reduced opioid consumption as compared to the routine conventional opioid anaesthesia. Opioid-free anaesthesia can serve as an alternative for selected patients with unwanted side-effects due to opioids.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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ORIGINAL ARTICLE
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Determinants of health-related quality of life in south indian patients with rheumatoid arthritis: A structural equation modeling approach

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Abstract

Introduction: The burden associated with rheumatoid arthritis (RA) is substantial, leading to pain, suffering, impaired physical function, disability and deterioration in quality of life of the patients. Very few studies evaluating health-related quality of life (HRQOL) and its determinants have been published among RA patients in Southern India. The aim of the present study is to investigate the various dimensions of HRQOL and its relationship with various sociodemographic characteristics, functional status and disease activity using a structural equation modeling (SEM) approach in patients with RA.
Materials and Methods: A cross-sectional study was conducted among 110 patients attending tertiary care teaching hospital. SF 36 was used to assess the HRQOL. Disease activity score-28 (DAS28) was used to measure the disease activity and Health Assessment Questionnaire Disability Index (HAQ-DI) was used for measurement of functional disability. SEM analysis was performed to test and evaluate the structural relationships of the model using R Programming.
Results: The mean age of patients was 44.85 ± 11.25 years and 92 (83.6%) were female. Lower HRQOL scores were obtained in the domain of role functioning/physical 48.86 (±40.55), general health 48.27 (±14.92) and physical functioning 40.45 (±23.76). SEM results showed that HAQ–DI and DAS28 were covariance with each other (r = 0.54, P = 0.039), HAQ-DI was a significant predictor of GenPHYS (P = 0.001) and DAS28 was a significant predictor of GenPHYS (P = 0.001) and GenMENT (0.025).
Conclusions: Impact of RA was substantial in both physical and mental domains of HRQOL. The functional disability was having an impact on physical health, whereas disease activity was associated with physical and mental health

domains of HRQOL.

Keywords: *Disease activity score 28, HAQ-DI, health-related quality of life, rheumatoid arthritis, structural equation modeling*

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Introduction

Rheumatoid arthritis (RA) is a chronic, symmetric polyarthritis causing joint damage that inevitably progressed to disability. The disease takes its toll on functional status of the patient leading to impaired physical function, and deterioration in quality of life. The public health burden associated with RA is substantial, including pain, suffering, increased health care utilization, significantly impacting the patients and their families.[1]

The health-related quality of life (HRQOL) is a multi-dimensional and subjective construct which includes the perception of a person's physical, psychological, social, and spiritual well-being in the context of their health conditions and treatment outcomes.[2] It is one of the powerful predictors of morbidity and mortality and is increasingly recognized as a crucial outcome in clinical practice and research. It has become a valid indicator of measuring the quality of health care delivery and treatment outcomes and shall be an integral part of health surveillance for better monitoring of disease burden especially in chronic diseases like RA. Its evaluation shall become a part of everyday clinical practice assessing the influence of disease and focusing on comprehensive care incorporating the bio-psycho-social aspect of a patient's health.[3],[4]

Several instruments have been developed to assess the quality of life and can broadly be categorized into global, generic, and disease-specific instruments.[5]

Studies have shown that there are several factors like socio-demographic, clinical, and psychosocial factors which affect all the aspects of the HRQOL. Age, gender, level of education, socioeconomic status (SES) showed an association with HRQOL.[6] Similarly, several diseases related factors like articular and extra-articular manifestations, disease activity, and functioning impairment, affect HRQOL adversely. Regular assessment of disease activity is crucial for the management of RA and instrument like disease activity score-28 (DAS28) is available for the assessment. However, the utility of DAS28 in evaluation of the disease activity has been grossly neglected in India.[4],[7]

Globally, around 3.4 million (95% UI 2.6–4.4) DALYs are attributed to RA and there is a significant increase in rates in the recent years.[8] In India, RA is predominantly affecting the rural areas and younger women. Limited data are available on evaluation of the overall burden of RA, and HRQOL significantly impacting the quality of care to such patients.[9]

There is an unmet need to sensitize the healthcare providers to understand the importance of various aspects of quality of life of patients suffering from RA and its correlates which will help them in predicting the course of illness and better monitoring of disease burden to plan and intervene to improve overall wellbeing of patients. Similarly, very few studies evaluating HRQOL among RA patients have been conducted in India especially in the southern part. Considering the epidemiological diversity within the country, the present study was aimed to investigate the various dimensions of HRQOL and its relationship with various demographic and clinical parameters, functional status and disease activity using a structural equation modeling (SEM) approach in RA patients attending the tertiary care hospital in south India.

Materials and Methods

Study design and setting

A hospital based cross-sectional study was conducted during October 2020–September 2021 among patients attending the rheumatology clinic, department of General Medicine of a tertiary care teaching institute.

Participants

The study sample consisted of patients having age >18 years, suffering from RA diagnosed by a Rheumatologist as per the American College of Rheumatology/European League Against Rheumatism 2010 criteria for RA classification.[10] Patients having co-morbid conditions, critically ill, pregnant females and patients not willing to participate were excluded from the study. A total of 110 patients participated in the study through convenient sampling. The approval from the Institutional Ethics Committee of the Institute was obtained before the starting the data collection (IEC approval No: VMCIEC/37/2019, Dated: September 18, 2019). The purpose of the study and nature of questions were explained to the patients and written informed consent was obtained.

Data sources/measurement

A semi-structured questionnaire was administered to the patients which consisted of socio-demographic characteristics, clinical parameters and medication details. The Medical Outcomes Study Short-Form Health Survey (SF-36) was used to

assess the HRQOL, DAS28 was used to measure the disease activity and Indian version of the HAQ-DI was used for the measurement of functional disability among the patients.

SF 36 is a disease-independent tool used to assess health outcomes among patients suffering from various chronic diseases like RA and has been extensively used in several countries including India. It captures 8 different health concepts viz. physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health (GH) perceptions. In SF-36 analysis, the raw scores are converted into transformed score on a 0–100 range for 8 subscales wherein the high score defines a more favorable health state or a better quality of life.[11],[12],[13]

The Stanford Health Assessment Questionnaire is a popular instruments used globally for assessing the patient's level of functional ability in many disease areas, including RA. The current study utilized the Indian version of Health Assessment Questionnaire Disability Index, which has shown to have a very good sensitivity, test-retest reliability and construct validity. It consists of total 12 questions relevant to the Indian population and the total scores obtained divided by 12 gave the disability Index (range 0–3) with the higher score reflecting the greater level of disability.[14],[15]

The DAS28 was utilized to assess the RA disease activity. It is a simple and widely used instrument for monitoring of disease activity in daily clinical practice consisted of measurement of a 28 tender joint count, a 28 swollen joint count, erythrocyte sedimentation rate or C-reactive protein, and a GH assessment on a visual analog scale. The overall range of the scores for DAS28 is 0–9.4. The level of RA disease activity can be interpreted as low if a DAS28 score is ≤3.2, a moderate disease activity if the score is between 3.2 and ≤5.1 and high disease activity for score >5.1. A score <2.6 corresponds with being in remission according to the American Rheumatism Association criteria.[16],[17]

Statistical methods

We analyzed the data using R Programming. The SES of the patient was calculated using the modified BG Prasad's classification and anemia status was determined according to the cutoff values recommended by the World Health Organization. Anemia was considered for males with hemoglobin <13 g/dL and females <12 g/dL.[18],[19] Cause and effect relationship of observed variables such as socio-demographic variables, disability index, DAS28 and HRQOL of RA patients is assessed by multiple linear regression models. The regression model included the various domains of HRQOL as a dependent variable and DAS28, duration of illness, HAQ-DI and SES as independent variables. Invariance and multicollinearity of the endogenous variables and structural relationship of latent variables are dealt with the aid of SEM. The latent variable “GenPHYS” was composed of four subscales of the SF-36 which includes physical functioning, role functioning/physical, bodily pain and role functioning/emotional whereas the latent variable “GenMENT” was composed of the subscales consisting of GH, social functioning, emotional wellbeing and energy/fatigue.[20],[21] HAQ-DI, DAS28, socio-demographic and clinical characteristics of the patients were selected as manifest variables. The relationship between manifest variables and latent variables were assessed using SEM.

Results

Of the 110 patients, 92 (83.6%) were female. The mean age of the patients was 44.85 ± 11.25 years. The majority 81 (73.6%) had completed their education up to school level (higher secondary education). As per BG Prasad classification 75 (68.2%) belonged to the middle class and 2 (1.8%) were belonged to an upper class. The mean body mass index scores of the patients was 25.43 (±4.35) and around 56 (51%) were overweight/obese. The majority of patients were suffering from RA for a period of 1–5 years 58 (52.7%) and more than 5 years 39 (35.5%). The majority of the patients 105 (95.5%) had articular manifestation, 10 (9.1%) of the patients had extra articular manifestation and 74 (67.3%) were anemic [Table 1].

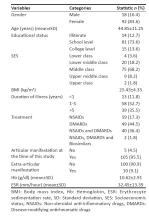

Table 1: Sociodemographic and clinical characteristics of rheumatoid arthritis patients

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[Table 2] shows the HRQOL-SF36, DAS28 and HAQ-DI scores of the patients. Quality of health indicators such as social functioning, role functioning/emotional, emotional well-being, energy/fatigue and pain had the higher scores like 61.82 (±23.39), 60.61 (±42.16), 58.76 (±13.35), 57.14 (±16.30) and 52.14 (±26.99) respectively when compared with the other subscales of SF 36 like role functioning/physical 48.86 (±40.55), GH 48.27 (±14.92) and physical functioning 40.45 (±23.76) which had the lower scores. The mean DAS28 score was 4.82 (±1.05) and the majority of them 75 (68.2%) were having moderate disease activity. The mean HAQ-DI score was 1.63 (±0.91) and a total of 52 (47.3%) were having severe disabilities.

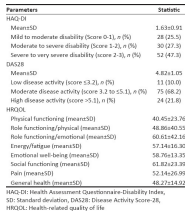

Table 2: Mean scores of Health Assessment Questionnaire-Disability Index, Disease Activity Score-28 and health-related quality of life in rheumatoid arthritis patients

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[Table 3] shows the multiple linear models of HRQOL of RA patients. The model specified that age and gender are the

least important independent variables and hence excluded from the model. Physical functioning of the RA patients was significantly associated with duration of illness (1–5 years-β = −16.27; *P* = 0.001, >5 years -β = −28.05; *P* = 0.001), DAS28 (β = −12.68; *P* = 0.000), HAQ-DI (β = −3.66; *P* = 0.000) scores.

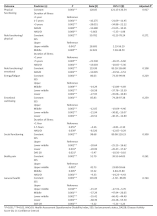

Table 3: Impact of sociodemographic variables, Health Assessment Questionnaire-Disability Index and Disease Activity Score-28 on the Health-related quality of life using multiple linear models

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Role functioning/physical of the RA patients was associated with SES, duration of illness, and HAQ-DI. More than 5 years of duration of illness was negatively associated with role functioning/physical (β = −21.53; *P* = 0.005). Similarly, upper middle (β = 28.69; *P* = 0.041), and middle class status (β = 22.82; *P* = 0.005), were positively associated with role functioning/physical.

Additionally, high DAS28 scores were significant predictors of several HRQOL domains like role functioning/emotional (β = −12.04; *P* = 0.002), social functioning (β = −5.47; *P* = 0.021), and GH (β = −3.22; *P* = 0.002), whereas high HAQ-DI scores were significantly associated with emotional wellbeing (β = −8.32; *P* = 0.039), and bodily pain (β = −9.33; *P* = 0.001).

Lower SES was significantly associated with the reduced scores of energy/fatigue (β = −27.95; *P* = 0.002), emotional well-being (β = −26.52; *P* = 0.001), social functioning (β = −20.99; *P* = 0.041) and GH (β = −68.39; *P* = 0.001), whereas duration of illness was found to be associated with reduced scores in emotional well-being (β = −4.36; *P* = 0.055).

[Table 4] includes two structural equation models, evaluating the relationship between the various factors and HRQOL. Model 1 has four manifest variables such as HAQ-DI, DAS28, SES and Duration of illness and two latent variables such as GenPHYS and GenMENT. These subscales were significantly associated with the latent variables in both the models.

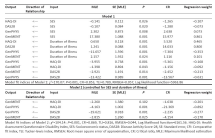

Table 4: Estimated coefficients from structural equation modeling for health related quality of life among rheumatoid arthritis patient

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In the model 1, SES was significantly associated with HAQ-DI (*P* = 0.026) and DAS28 (*P* = 0.020) as well as with GenPHYS (*P* = 0.008) and GenMENT (*P* = 0.001). Similarly, duration of illness was also associated with HAQ-DI and DAS28, GenPHYS and GenMENT (*P* = 0.001, 0.001, 0.001, 0.024 respectively).

HAQ-DI was significantly associated with GenPHYS and GenMENT (*P*= 0.001, 0.043) and DAS28 was also found to be associated with GenPHYS and GenMENT (*P* = 0.001, 0.014). The model fit indices of model 1 (χ^2 = 170.07: *P* = 0.001; Comparative Fit Index (CFI) = 0.853, Tucker-Lewis index (TLI): 0.789; Root Mean Square Error of Approximation (RMSEA) = 0.057) reveal that the model 1 was reasonably fit [Figure 1].

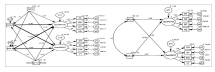

Figure 1: Model 1: Structural equation models of the relationship between HAQ DI, DAS28, and HRQOL in RA Patients. Circles represent latent variables (GenPHYS and GenMENT) and squares represent observed variables (SF 36 scales). Model 2: Structural equation models of the relationship between HAQ DI, DAS28, and HRQOL in RA Patients after controlling for SES and Duration of illness. PF: Physical functioning, RP: Role Physical, BP- Bodily Pain, RE Role emotional, GH: General health, SF: Social functioning, EW: Emotional well being, VT: Vitality, SES: Socioeconomic status, HAQ DI: Health Assessment Questionnaire Disability Index, HRQOL: Health related quality of life, RA: Rheumatoid arthritis

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Model 2 is the nested model of the model 1 in which we controlled the effect of SES and duration of illness which were considered as confounding variables. It is observed that HAQ-DI is a significant predictor of GenPHYS (*P* = 0.001) whereas DAS28 is a significant predictor of GenPHYS as well as GenMENT (*P* = 0.001, 0.025). Similarly HAQ–DI and DAS28 were covariance with each other (*r* = 0.54,*P*= 0.039).

The model fit indices of model 2 (χ^2 = 104.14: *P* = 0.001; CFI = 0.869; TLI =0.816 RMSEA = 0.044) reveal that the model 2 was a better fit [Figure 1].

Therefore, HAQ-DI and DAS28 predict the GenPHYS whereas DAS28 predict GenMENT irrespective of SES and duration of illness.

Discussion

In our study, we obtained lower scores in the domain of role functioning/physical, GH and physical functioning as compared with other subscale of the SF 36. This is similar to the findings of the other studies which reported the physical domain as a most affected domain of HRQOL.[4],[12] A systematic review and meta-analysis done by Matcham *et al*., showed that RA negatively impacts HRQOL and the impact is more severe on physical HRQOL domains as compared

with mental well-being[13] A strong social support, especially from the family members may be attributed to the higher scores of social functioning and emotional wellbeing in Indian patients with RA.

We observed moderate disease activity among the majority of the patients (68.2%) and almost half of them (47.3%) presented with a severe functional disability. The intensity of disease activity observed among our patient is lesser as compared with the other Indian studies in which the assessment was done at the initial presentation and this reduction can be attributed to the impact of their treatment over a period of time.[7],[22]

We performed the multiple linear regression analyses to evaluate the impact of various socio-demographic variables, functional disability and disease activity on the HRQOL. High HAQ-DI scores were significant predictors of several HRQOL domains like physical functioning, role functioning/physical and bodily pain, whereas high DAS28 scores were significantly associated with physical functioning, role functioning/emotional, social functioning and GH. Socio-economic status was found to be directly associated with all domains of HRQOL except physical functioning with lower classes reflecting the poorer quality of life among the patients.

In this study, we constructed models to exhibit the relationship between several distinct variables and the domains of HRQOL among patients with RA. Most of the authors have used the correlation analysis for evaluating the various factors affecting HRQOL of RA patient.[23],[24] To our knowledge, this study is first of its kind which focuses on establishing the relationships among these variables using a SEM among south Indian patients suffering from RA. SEM is the better tool for analyzing the latent variables. In addition, through SEM analysis, we can test and evaluate multivariate causal relationships. Through this approach we found SES and duration of illness as well as DAS28 and HAQ-DI are associated with HRQOL. While components of SES (income, education, etc.) act as potential confounders, few studies have investigated and proved the causal effect of SES on HRQOL and its role in disease related outcome should be viewed carefully.[25] People belonging to lower socio-economic status confront several barriers, including availability; accessibility and affordability to health care services leading to detrimental consequences in the long run, which often are reflected in poor self-reported outcomes like disability, quality of life and disease activity indices. Similarly, longer duration of illness was found to be negatively associated with the domains of physical and emotional well being. These findings are similar to the findings of other studies in India as well as other countries.[23],[24],[25]

We obtained an inverse relationship between HAQ-DI and DAS28 with HRQOL with a greater level of disability and high disease activity leading to lower scores in GenPHYS and GenMENT resulting in poor quality of life. Several studies have shown the strong correlation between high disease activity and disability with a physical component, and mental components of HRQOL. Although we have adopted a different methodology of analysis, our finding reaffirms the earlier findings. After controlling the effect of SES and duration of illness the association between DAS28 and GenPHYS and GenMENT persists whereas HAQ-DI found to have no impact on the mental component of HRQOL. In spite of the limitation of mobility and activities, the interplay of variety of factors like social support, coping strategies and disease acceptance plays an important role in psychosocial adjustment among individuals, enabling them to adapt to the demands of the chronically ill disease and disabilities leading to better psychological well-being.[26] In the present study, we obtained better scores in the domain of social functioning, however to substantiate the optimal social support, we need further exploration using a multidimensional measure of social support among RA Patients to understand its effect on the psychological wellbeing of the patients.

Limitations

The results of the study should be viewed carefully as we sampled the patients from a single hospital with relatively small sample size, which limits the generalisability of its findings to a broader population in the community. Similarly, no causal relationship can be ascertained between various factors and HRQOL by virtue of the observational nature of the study. Further exploratory studies are required to evaluate the factors like concomitant nutritional deficiency, community acquired infections, lower educational status, which are inextricably linked with lower SES.

Conclusions

The substantial impact of RA was observed in both physical and mental domains of HRQOL. The findings of this study are helpful in gaining an insight into the various factors and its inter-relationship using a structural equation model. The level of disability was having an impact on physical health, whereas disease activity was inversely associated with physical and mental health domains of HRQOL after controlling the effect of SES and duration of disease. To improve the overall health of the patient, it is crucial to assess patients and intervene appropriately through a multidisciplinary approach that will improve the long term health of the patients.

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Nil.

Conflict of interest

There are no conflicts of interest.

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Figures

[Figure 1]

Tables

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Clinical features, severity and outcome of acute pancreatitis in systemic lupus erythematosus

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Abstract

Acute pancreatitis (AP) is a rare but life threatening manifestation of Systemic Lupus Erythematosus (SLE). The current study aims to study the clinical characteristics, severity, mortality, and outcome of SLE-related AP in Indian population. We retrospectively reviewed medical records of patients with SLE who had AP in the past. Data from 13 rheumatology centers across India were compiled. All patients satisfied SLICC criteria for SLE and ATLANTA criteria for AP. AP was classified in to mild, moderate and severe using revised Atlanta classification. Patients with known risk factors like gall stone and alcohol were excluded.Sixty-six patients (six, children) were studied. Majority of patients were females (82%). The median age of presentation was 24 (11–63) years and most patients (57.5%) presented within first year of diagnosis of lupus. AP occurred mostly in the setting of active lupus (89%). Active nephritis was seen in 39% while a fourth had CNS disease. Patients with severe AP had lower C3. Ascites and sepsis were most common local and systemic complications, respectively. Mortality was 17%. Hypocalcemia, presence of sepsis and shock predicted mortality. In the multivariate analysis, only presence of shock remained as independent predictor of death (OR 63.0, 95% CI: 5.2–760.3). Pancreatitis is an early manifestation of SLE and is associated with active disease. Significant mortality is seen particularly with severe pancreatitis.

Keywords Systemic lupus erythematosus · Acute pancreatitis · Gastrointestinal

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder affecting various organs and organ systems. Gastrointestinal manifestations of SLE vary from mild serositis and elevated liver enzymes to potentially life-threatening condition like mesenteric vasculitis. Acute pancreatitis (AP) is a rare, albeit serious manifestation of SLE [1]. The reported incidence varies from 1–5% [2–5]. Etiology could be multi-factorial and is more commonly due to secondary causes like an infection, or drugs [6] commonly used for

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lupus like steroids [7], and azathioprine [8, 9]. Rarity of the disease and acute pancreatitis make it more challenging for a treating physician to diagnose and manage these patients. Outcome is variable and often affected by the delay in reaching diagnosis. This could be particularly challenging when pancreatitis is a presenting manifestation of SLE [3]. Data on AP in SLE from India are limited to a few case reports and small case series. The current study aimed to study the clinical characteristics, severity, outcome and predictors of mortality of SLE-related AP in Indian population.

Methods

We retrospectively reviewed medical records of patients with SLE who had AP in the past from 13 rheumatology centers across India. Patients who fulfilled SLICC criteria for lupus were enrolled [10]. Some of these cases have been previously reported [7, 11]. Active lupus was defined as SLEDAI > 3 [12]. Renal involvement was defined as presence of proteinuria (0.5 g/24 h), active sediments in urine or biopsy evidence of lupus nephritis. Central nervous system (CNS) involvement was defined as presence of any one of 19 neuropsychiatric syndromes defined by American College of Rheumatology (ACR) 1999 definitions [13]. Diagnosis of AP required presence of two of the following three criteria: acute onset epigastric pain, elevation in serum lipase or amylase (≥ 3 times upper limit of normal) and characteristic findings of acute pancreatitis on imaging [14]. Demographic details, clinical characteristics, treatment and outcome were recorded. Patients who had known risk factors for AP like gall stone, and alcohol were excluded.

AP was classified to mild (absence of organ failure or local systemic complication), moderate (transient organ failure of < 48 h and/or local/systemic complications) and severe (organ failure > 48 h) according to Atlanta severity grading [14]. Mild and moderate were clubbed together in non-severe category and compared with severe AP.

Statistics

Comparison was done between severe and non-severe AP. Chi square was used for categorical variables. Mann Whitney *U* test was used to compare medians. p value < 0.05 was taken as significant. Comparison was also made between patients who died and survived to identify predictors of mortality. Binary logistic regression was performed using variables that were significant in univariate analysis to identify independent predictors of mortality. All statistics were done using SPSS (v21, IBM).

The study was approved by institute ethics committee and waiver of consent was obtained as it was retrospective data-based study (IEC 2020-278-DM-EXP-31). No funding was received for this study.

Results

Data of 66 patients (6, children) of SLE who had acute pancreatitis were compiled. Majority of patients were females (81.8%). The median age at presentation was 24 (11–63) years. Median duration of lupus at the time of onset was 12 (0–156) months. More than half of the patients presented within first year of diagnosis of lupus (57.5%). Four patients had AP as one of the presenting manifestations of SLE. At the time of diagnosis of AP, median SLEDAI was 18 (0–32) with 89.3% patients showing active disease (SLEDAI > 3). Amongst the extra-gastrointestinal manifestations, 39.4% had nephritis while a fourth had CNS disease. Forty-three patients were on corticosteroids, five on cyclophosphamide, six on azathioprine and five were getting MMF at the time of AP (Table 1).

All patients had abdominal pain as the presenting manifestation of AP. Other manifestations of AP included abdominal distension (60.6%), vomiting (66.7%) and jaundice (7.6%). Fifty-two patients (78.8%) had elevated enzymes and 60 (90.1%) had evidence of AP on imaging (Fig. 1).

Severity of AP

According to ATLANTA classification, 26 patients (39.4%) had mild, 18 (27.3%) had moderate and 22(33.3%) had severe AP. Percentage of patients with low C3 levels were higher in severe AP when compared with non-severe AP (p: 0.013, OR: 5.23 95% CI:1.34–20.40). There were no significant differences in other clinical or laboratory parameters between severe and non-severe groups. More number of patients in severe AP group received pulse methyl prednisolone than non-severe group (81.0 vs 53.5%, p: 0.053). Number of patients who received cyclophosphamide were comparable in both groups (42.9 vs 34.1.0%, p: 0.586) (Table 2).

Treatment and outcome

Most patients received immunosuppression [oral prednisolone (96.9%), IV methylprednisolone or dexamethasone (62.5%), or cyclophosphamide (36.9%)]. Local complications of pancreatitis included ascites (18), pleural effusion (17), necrotizing pancreatitis (2), and pseudocyst (1). Among systemic complications, 19 had sepsis (3 culture positive), and 15 patients had acute respiratory distress syndrome (ARDS). Eleven patients with severe AP (50%) died of multiorgan failure. Serum calcium level (corrected for albumin) at presentation was significantly lower in patients who died [6.75 (5.20–7.70) vs 7.90 (5.40–9.90), p: 0.001).

Table 1 Clinical features, laboratory parameters and treatment received by lupus pancreatitis patients

Age, in years	24 (11–63)
Male: female	12:54
Duration, in months	12 (0–156)
Clinical features of lupus	
SLEDAI	18 (0–32)
Active lupus[a]	59 (89.3%)
Nephritis	26 (39.4%)
NPSLE	17 (25.8%)
Musculoskeletal	41 (62.1%)
Mucocutaneous	50 (75.8%)
Clinical features of pancreatitis	
Abdominal pain	66 (100%)
Vomiting	44 (66.7%)
Abdominal distention	40 (60.6%)
Jaundice	5 (7.6%)
Fever	40 (50.6%)
Concomitant medications	
Steroid	43 (65.2%)
Steroid dose, mg/day	13.4 ± 19.3
Azathioprine	6(9.1%)
MMF	5(7.6%)
Cyclophosphamide	5(7.6%)
Laboratory parameters	
Haemoglobin, g/dL	8.6 (5.7–13.0)
Leukocyte count, per mm^3	6870 (600–23,100)
Platelet count, $\times 10^5$ per mm^3	1.45 (0.12–4.70)
AST, IU/mL	67.5 (8.0–706.0)
ALT, IU/mL	52.5 (10.0–1504)
Total Bilirubin, mg/dL	0.6 (0.1–8.3)
Serum Creatinine, mg/dL	0.9 (0.15–3.70)
Serum Albumin, mg/dL	2.6 (1.2–4.2)
Serum Amylase, IU/mL	607 (40–7600)
Serum Lipase, IU/mL	821.5 (33–12,977)
Serum Calcium	7.8 (5.2–9.9)
C3	48 (10–160)
C4	9 (3–70)
ds DNA	178 (0–500)
Treatment received for AP	
Methyl prednisolone/dexamethasone pulse	40 (62.5%)
Any steroid(oral or parenteral)	63 (96.9%)
CYC	24 (36.9%)

Categorical variables expressed as *n* (%)

Continuous variables expressed as mean ± SD

Presence of sepsis (OR:10.4 95% CI:2.36–45.9) and shock (OR:80.0, 95% CI:8.7–739.5) also predicted death. Other clinical characteristics and laboratory findings were similar in both groups (Table 3). In the multivariate analysis, only presence of shock remained as independent predictor of death (OR 63.0, 95% CI: 5.2–760.3). On a follow up of 147.8 patient years (median follow-up 22 months), two patients had recurrence of acute pancreatitis, two patients developed diabetes while one had malabsorption.

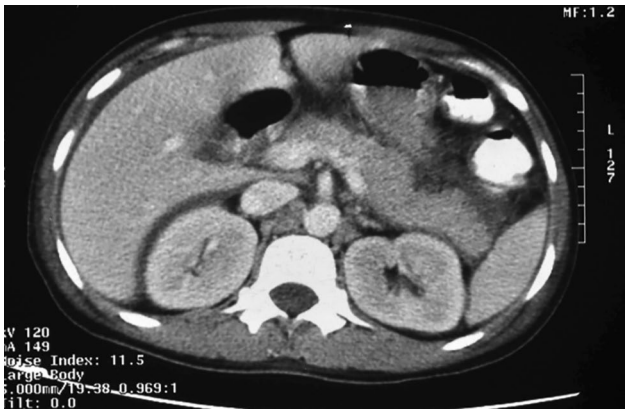

Fig. 1 Contrast enhanced computed tomography showing bulky pancreas in a lupus patient with acute pancreatitis

Discussion

This is the largest series of pancreatitis due to lupus from India looking at severity, mortality and the predictors of these outcomes in AP. It is an early manifestation of lupus most commonly seen within the first year of diagnosis and often goes parallel with lupus activity. There is no correlation with serology except in severe cases when complements can be low. Course is often compounded by local and systemic complications with higher mortality in severe cases. Most commonly used drugs for management included steroids and cyclophosphamide.

Abdominal pain is a common symptom in SLE with a prevalence varying from 8–40% [15]. This could be due to multiple reasons from less sinister ones like gastritis to more serious ones like acute pancreatitis. Latter, however, is a rare complication of SLE with a varying prevalence 0.6–0.9% [1, 16] to 3.5% [17]. Table 4 highlights major studies on AP in SLE. Etiology of AP in a lupus patient is often difficult to ascertain. Coexisting traditional risk factors for AP including alcohol, gall stones, hypercalcemia and hypertriglyceridemia should be ruled out. In the absence of a definite risk factor, especially in setting of active manifestations of lupus in other organs, etiology of AP is ascribed to SLE [4].

Mechanisms postulated for AP in lupus include vasculitis, immune complex deposition, microinfarction and ischemia [4]. In addition, increased viscidity of pancreatic juice, decreased pancreatic juice bicarbonate, decreased amylase secretion and precipitation of immune complexes in pancreatic duct were proposed as cause of steroid induced pancreatitis [18, 19]. Histopathology from autopsy and surgical

Table 2 Comparison between severe and non-severe AP

	Severe AP ($n=22$)	Non Severe AP ($n=44$)	p
Age, in years	26 (15–50)	24 (11–63)	0.383
Male: female	4:18	8:36	0.999
Duration, in months	13.5 (1–156)	9.5 (0–132)	0.357
SLEDAI	19 (8–31)	18 (0–32)	0.296
Active disease	19 (100%)	40(95.3%)	0.999
Renal	9 (40.9%)	17 (38.6%)	0.999
NPSLE	8 (36.4%)	9 (20.5%)	0.233
Musculoskeletal	17 (77.3%)	24 (54.5%)	0.107
Mucocutaneous	19 (86.4%)	31 (70.5%)	0.226
Abdominal pain	22 (100%)	44 (100%)	0.999
Abdominal distention	19 (86.4%)	21 (47.7%)	0.003
Vomiting	16 (72.7%)	28 (63.6%)	0.583
Jaundice	1 (4.5%)	4 (9.1%)	0.658
Fever	16 (72.7%)	24 (54.5%)	0.188
Hemoglobin, g/dL	8.9 (6.2–11.8)	8.4 (5.7–13.0)	0.765
Leukocyte count/mm^3	7240 (1400–23,000)	6380 (600–23,100)	0.344
Platelet, $\times 10^5/mm^3$	1.0 (0.26–4.7)	1.5 (0.12–3.90)	0.076
AST, IU/mL	80 (15–706)	55.5 (8- 600)	0.400
ALT, IU/mL	66 (11–698)	51 (10–1504)	0.347
Total bilirubin, mg/dL	0.8 (0.2–2.9)	0.6 (0.1–8.29)	0.049
Serum creatinine, mg/dL	1.1 (0.15–3.70)	0.80 (0.15–2.0)	0.006
Serum Albumin	2.45 (1.2–3.6)	2.6 (1.15–4.2)	0.419
Serum Amylase, IU/mL	690 (135–2878)	570.5 (40–7600)	0.465
Serum lipase, IU/mL	698 (148–12,977)	1205 (33–12,569)	0.431
Serum calcium, mg/dL	7.2 (5.2–9.5)	7.9 (5.4–9.9)	0.061
Low C3	40 (26–86)	54 (10–160)	**0.182**
Low C4	9 (3–28)	10 (3–70)	**0.108**
High ds DNA	220 (0–500)	80 (0–500)	0.283

Categorical variables expressed as n (%)

Continuous variables expressed as mean ± SD

specimen shows inflammatory infiltrates and necrosis. Vascular lesions including thrombosis and vasculitis are rare [4]. These histopathologic features are indistinguishable from pancreatitis due to other causes.

The median age of onset of AP in our study was 24 (11–63) years, similar to most of other studies [1, 3, 20] though in an inception cohort of lupus from India, the median age at onset was 27 years [21]. A retrospective study comparing adult and childhood lupus associated AP showed a significantly higher frequency of AP in childhood SLE (3.3 vs 1.1%) [22]. Our series only had six children (four, female) with median age of 14 (11–16) years. A recent narrative biomedical review of 264 cases from 11 articles observed a tendency of AP occurrence in initial 3 years of diagnosis of SLE [18]. In our study, more than half of patients developed AP in first year of disease.

Most cases of AP occurred in the setting of active lupus. This suggests that lupus-related autoimmunity may be the cause of AP. However, these patients usually are on high dose glucocorticoids, which itself is a known cause for AP [7]. It becomes challenging to determine the etiology of AP in such scenario. Occurrence of AP as the presenting feature of SLE in a steroid naïve further supports the role of lupus-related mechanisms in development of AP. Further, majority of patients with AP related to SLE are treated with steroids safely suggesting that steroids have minor role if at all, in development of AP. Furthermore, discontinuation of steroids was identified as a risk factor for development of AP in an Indian study of 11 patients with AP [23].

Most patients had other active manifestations of SLE including nephritis, mucocutaneous, musculoskeletal and CNS involvement when presenting with AP. Serological markers indicating active disease were also observed in most patients. In our series, levels of C3 correlated with severity of AP. Previous studies have shown association of hypertriglyceridemia, psychosis and pleuritis with lupus associated AP [3]. In an Indian study, seizure and arthritis were significantly associated with lupus associated AP [23]. One

Table 3 Comparison between mortality and non-mortality group

	Mortality($n=11$)	Non- Mortality($n=55$)	p
Age, in years	23 (15–46)	24 (11–63)	0.870
Male: female	3:8	9:46	0.406
Duration, in months	18 (3–156)	10 (0–132)	0.138
SLEDAI	19 (12–30)	18 (0–32)	0.468
Active disease	9 (100%)	50 (96.2%)	0.999
Renal	4 (36.4%)	22 (40.0%)	0.999
NPSLE	4 (36.4%)	13 (23.6%)	0.454
Musculoskeletal	9 (81.8%)	32 (58.2%)	0.185
Mucocutaneous	9 (81.8%)	41 (74.5%)	0.999
Pain	8 (100%)	51 (100%)	0.999
Abdominal Distention	11 (100%)	29 (52.7%)	0.002
Vomiting	8 (72.7%)	36 (65.5%)	0.739
Jaundice	0 (0%)	5 (9.1%)	0.580
Fever	10 (90.9%)	30 (54.5%)	0.040
Shock	**10 (90.0%)**	**6 (11.1%)**	**< 0.001**
Sepsis	**8 (72.7%)**	**11 (20.4%)**	**0.001**
ARDS	9 (81.8%)	6 (11.1%)	< 0.001
Pseudocyst	0 (0%)	1 (1.9%)	0.999
Ascites	2 (28.6%)	16 (33.3%)	0.999
Pleural effusion	3 (37.5%)	14 (28.6%)	0.635
Laboratory findings			
Haemoglobin, mg/dL	8.9 (6.2–11.8)	8.5 (5.7–13.0)	0.843
Leukocyte count/mm^3	7700 (1400–17,000)	6500 (600–23,100)	0.434
Platelet, $\times 10^5$per mm^3	1.4 (0.36–4.70)	1.48 (0.12–3.90)	0.897
AST, IU/mL	83 (21–706)	63 (10–600)	0.581
ALT, IU/mL	66 (25–698)	52 (10–1504)	0.369
Total Bilirubin, mg/dL	0.8 (0.2–2.9)	0.6 (0.1–8.3)	0.458
Serum Creatine, mg/dL	1.4 (0.15–3.70)	0.87 (0.15–2.60)	0.024
Serum Albumin, mg/dL	2.7 (1.2–3.4)	2.5 (1.2–4.2)	0.737
Serum Amylase, IU/mL	789 (206–2878)	604 (40–7600)	0.516
Serum Lipase, IU/mL	814 (148–12,977)	829 (33–12,569)	0.938
Serum calcium, mg/dL	**6.75 (5.2–7.70)**	**7.9 (5.4–9.90)**	**0.001**
Low C3	**35 (27–86)**	50 (10–160)	0.444
Low C4	9 (4–28)	9 (3–71)	0.925
High ds DNA	280 (0–500)	128 (0–500)	0.222

Categorical variables expressed as n (%)

Continuous variables expressed as mean ± SD

fourth of our patients had active CNS lupus but numbers were small to look for these associations in our study.

Presentation of AP in SLE did not substantially differ as compared to pancreatitis due to other etiologies. Abdominal pain is the most common presenting symptom [24]. Characteristically this pain radiates to back and gets aggravated by food intake. Other symptoms include abdominal distention, vomiting and rarely jaundice [25]. A minority of patients, 5–10%, can present without pain [26], though all our patients reported pain. There may be a higher probability of lupus patients presenting without pain as a number of these patients are on high dose steroids. Steroids can mask some of these abdominal symptoms and signs. High index of suspicion in patients with otherwise inexplicable abdominal complaints and respiratory distress is needed. The diagnosis of AP can be confirmed by measuring enzyme levels and imaging.

Imaging helps in making diagnosis of AP in the absence of typical pain or elevated enzymes. Abdominal ultrasound may show evidence of bulky pancreas, peripancreatic inflammation and increased vascularity [27]. Ultrasound also helps in identifying other causes of AP like gall stones, structural anomalies and local complications like pseudocyst, ascites and abdominal collections. CT is usually

Table 4 Major case series on SLE related AP

Study	Country	Number of patients with AP	Mean Age	Male:female	Lupus activity	Concomitant Medicines	AP	Treatment	Outcome
Derk et al. 2004 [5]	USA	25 in 2947 SLE patients	44	2:20	Nephritis 56% Arthritis 44%	Steroid 92% Mean steroid dose 18.5 mg/d	Abdominal pain 84% Distention 60% Vomiting 52%		Pseudocyst 12% ARDS 8% Sepsis 8% Death 16%
Pascaul-Ramos et al 2004 [17]	Mexico	35 in 895 SLE patients	30	2:33		Steroid 65%			Death 14%
Makol et al. 2010 [3]	USA	63 in 1811 SLE patients	–	2:61	Nephritis 27% NPSLE 18% Mucocutaneous 70% Low C3 56% Low C4 48% ds DNA 52%	Azathioprine 8% MMF 2% CP 3%			Pseudocyst 10% Death 3.2%
Wang et al. 2011 [20]	Taiwan	40 in 2976 SLE patients	31.18	2:38	Mean SLEDAI: 16.1 Active disease:92.5% Proteinuria: 69.7% Thrombocytopenia: 55% CNS: 22.5% High ds DNA: 86.2% Low C3:85.3% Low C4: 58.8%	Steroid 60% Azathioprine: 7.5%	Abdominal pain: 97.5% Vomiting: 67.5% Fever: 57.5%	Steroid: 90%	Infection:12.55 Pulmonary hemorrhage:2.5% Death: 27.5%
Yang et al. 2012 [1]	China	27 in 4053 SLE patients	26.9	2:25	Mean SLEDAI 21.7 Nephritis 89% NPSLE 26% Hematological 100% Mucocutaneous 67% Musculoskeletal 59% Low C3 100% Low C4 81% High ds DNA 90%	Steroid 96% Azathioprine 7% CP 18%	Abdominal pain 93% Vomiting 74%	Steroid: 93%	Death 37%
Gormezano et al. 2015 [22]	Brazil	33 in 2192 SLE patients	25.9	5:28		Steroid 97% Azathioprine 21% MMF 18%	Abdominal pain 67% Vomiting 61% Fever 67%	CP: 18%	Death 12%

Table 4 (continued)

Study	Country	Number of patients with AP	Mean Age	Male:female	Lupus activity	Concomitant Medicines	AP	Treatment	Outcome
Yi-Kai et al. (2016) [31]	China	26	34.9	4:22	Mean SLEDAI 14.3 Nephritis 72% NPSLE 17% Hematological 61% Mucocutaneous 33% Musculoskeletal 28% Low C3 72% Low C4 78% High ds DNA 78%	Mean steroid dose 33.4 mg/d MMF 35% CP 23%			Pseudocyst 11% Ascites 6% Death 31%
Wang et al. (2016) [16]	China	46 in 5665 SLE patients	31	6:40	Mean SLEDAI 17 Low C3 96% Low C4 96% High ds DNA 67%		Abdominal pain 89% Vomiting 43% Jaundice 15%		Pseudocyst 12% Sepsis 20% Death 32.6%
Current, (2019)	India	66	27.1	12:54	Mean SLEDAI 18.1 Nephritis 39% NPSLE 26% Mucocutaneous 76% Musculoskeletal 62% Low C3 66% Low C4 64% High ds DNA 62.5%	Steroid 65% Mean steroid dose 13.4 mg/d Azathioprine 9% MMF 8% CP 8%	Abdominal pain 100% Distention 60% Vomiting 44% Jaundice 8% Fever 51%	Steroid: 97% CP: 36.9%	Pseudocyst 1.5% Ascites 27% Pleural effusion 26% ARDS 23% Sepsis 29% Shock 24% Death 17%

reserved for patients with diagnostic confusion. CT scan better characterizes complications like pancreatic edema, necrosis and peripancreatic fluid collections [27]. Severity of necrosis in CT can predict outcome of AP [28].

Current principles of management of AP includes pain management, aggressive fluid resuscitation, intensive monitoring and support of organ function [29]. An antibiotic restrictive policy should be adopted. There is no role for prophylactic antibiotics regardless of severity of AP [30]. All patients should be closely watched for development of complication including secondary infections. AP in lupus is usually treated with immunosuppression along with supportive management of pancreatitis, although not supported by high quality evidence [2]. Steroids are used in varying doses depending on severity. Azathioprine or cyclophosphamide are also used along with steroids. Glucocorticoid treatment was found to be associated with better prognosis SLE patients with AP in a study from South China [1]. Data from another Chinese study show addition of plasma exchange to steroid did not affect the outcome in lupus associated AP although it brought about reduction in inflammatory cytokines levels in plasma [31]. No data are available on recurrence of AP in SLE. In our study, only 3% (two patients) had recurrence. Thus, role of maintenance immunosuppression in lupus-related pancreatitis remains unclear.

Local complications of AP include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis. While local complications seemed to occur less frequently in lupus associated AP, systemic complications were more common than in AP due to other etiologies. Systemic complications include acute kidney injury, ARDS, sepsis and shock. Our cohort had third space collection as most common local complication. Sepsis followed by ARDS were seen as most common systemic complications occurring in nearly 30% patients. A rare complication of lupus associated AP is macrophage activation

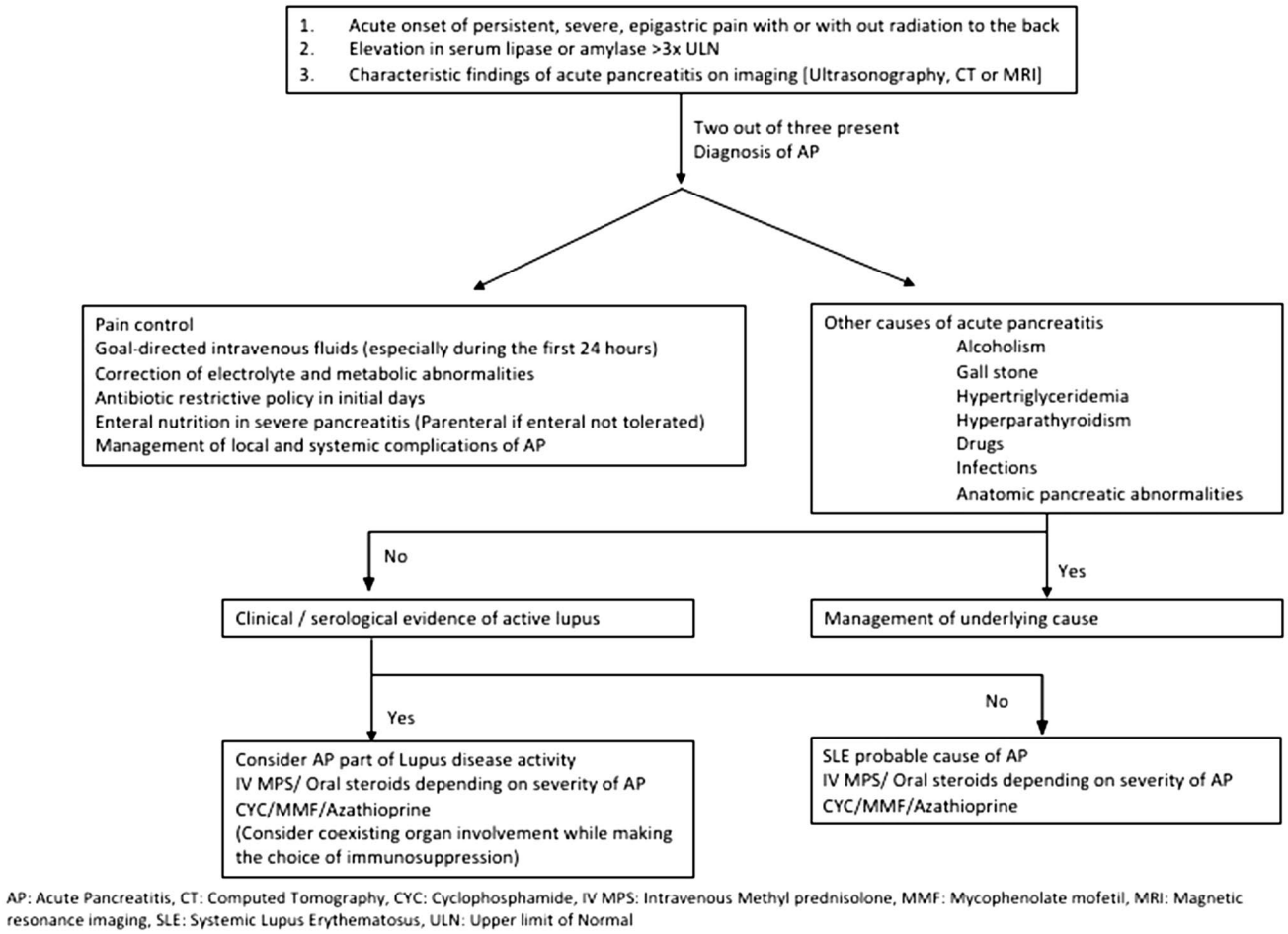

Fig. 2 Proposed algorithm for diagnosis and management of AP in SLE

syndrome (MAS) and is reported more commonly in childhood lupus associated AP [22]. None of our patients had MAS.

Mortality in our population was 16.67%. Mortality rates up to 27% were observed in the previous studies [16]. Mortality in lupus associated AP is higher than in AP due to other causes. A significantly high mortality in childhood lupus associated AP was observed in previous two retrospective studies [22, 32]. We found that serum calcium, presence of sepsis, shock and severe AP at presentation predicted death. Median serum calcium was significantly lower in patients who died than in patients who survived. A similar observation was made in earlier review of published case reports of 77 cases of lupus-related pancreatitis where hypocalcemia was associated with mortality [4]. Hypocalcemia is a marker of severe pancreatitis and hence this is not surprising. Thrombocytopenia, hypocomplementemia and elevated serum amylase are also associated with higher mortality. Mortality was associated with concurrent SLE symptoms, higher SLEDAI score at presentation of acute pancreatitis, severe AP and the presence of complications in a study from China [16]. In the multivariate analysis, only presence of shock at presentation, remained as independent predictor of death. We did not find disease activity measured by SLEDAI or serology to be a predictor of mortality but low C3 was associated with severe AP.

Diagnosis of pancreatitis continues to remain a challenge in SLE, despite abdominal pain being the most common presenting feature. Mortality is still high, despite use of immunosuppressive drugs. Based on available data as well as our observations, we propose an algorithm for diagnosis and management of AP in SLE (Fig. 2).

The strength of present study is the large number of patients with AP in SLE from a developing country which shows that the presentation and outcome are similar to that seen in developed world. The main limitation of this study is its retrospective nature. Management strategies may vary in across centers. Lack of detailed autoantibody profile made it difficult to see any association with APS. Further, no control group was included thus we could not identify predictors of AP in SLE.

Conclusions

Pancreatitis is an early manifestation of SLE and is associated with active disease. Significant mortality is seen particularly with severe pancreatitis.

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Original Article

Prospective Study of Patients with Inflammatory Back Pain, Clinical Characteristics and Treatment Response in Ankylosing Spondylitis in Two Centers of Rheumatology in South India

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Abstract

Introduction: Ankylosing spondylitis is inflammatory arthritis affecting the spine and peripheral joints more commonly in men of 15 years to 40 years of age and is a part of the spectrum of diseases called spondyloarthropathy. Psoriasis, uveitis, ulcerative colitis, and inflammatory bowel disease form part of the systemic manifestations. There exists a long delay between the onset of inflammatory back pain and being diagnosed with ankylosing spondylitis.

Methodology: We set out to study the clinical profile, diagnosis, and management of patients with spondyloarthritis (SpA) prospectively and follow-up over 2 years period. All patients who had inflammatory back pain and diagnosed to have SpA were included in this prospective study in two different centers of Rheumatology. Clinical characteristics, magnetic resonance imaging (MRI)-spine and sacroiliac joints, disease activity using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and early treatment response were assessed. Other investigations including bloods, X-rays, and screening for biologics were done as and when indicated. We used both synthetic Disease-Modifying AntiRheumatic Drugs (DMARDS) and biosimilars as per the British Society of Rheumatology guidelines and patient choice. Patients were reviewed every 3 months for 1–2 years. The response to treatment was assessed and compared with other studies.

Results: Forty -two patients were studied in this 2 years period (15 patients out of 57 lost to follow up). All patients had the diagnosis of ankylosing spondylitis as per Assessment of Spondylo Arthritis international Society (ASAS Score) criteria and MRI evidence of sacroiliitis and 22 patients had peripheral synovitis. HLA-B27 was positive in 11/19 patients. Eleven patients had been on anti-Tumor Necrosis Factor (TNF) drugs and 26 patients were on DMARDs. At the end of 24 weeks, disease activity indices including BASDAI and BASFI were low in remission and statistically significant. At the end of 2 years, most of them were in remission and 81% were continuing to work and maintain productivity. Patients who underwent treatment with biosimilar TNFs showed a significant reduction in disease activity and achieved remission earlier, as evidenced by BASDAI and BASFI scores, compared to others who were on DMARDS and supportive therapy. The usage of DMARDS was more than biosimilar drugs as they are expensive.

Conclusion: This study shows the real-world data on the diagnosis and management of patients with ankylosing spondylitis, achieving remission, and maintaining the work-life balance. Early diagnosis with MRI and appropriate intervention with DMARDS are the important factors in this study.

Key Words: *Ankylosing spondylitis, anti-tumor necrosis factor, bath ankylosing spondylitis disease activity index, bath ankylosing spondylitis functional index, biosimilars, inflammatory back pain*

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Introduction

Spondyloarthritis (SpA) is a spectrum of inflammatory arthritides in which ankylosing spondylitis is common with a worldwide prevalence of up to 0.9% including women.[1] Its etiology and pathogenesis are not yet fully understood. SpA is a family of systemic inflammatory rheumatic diseases that have been extensively reported and studied from India over the last four decades. The epidemiological studies estimate the prevalence of SpA to be 7–9/10,000 persons.[2,3] Several years may pass between the onset of symptoms and definite diagnosis. This delay is most likely due to low awareness of AS or SpA among non rheumatologist and the fact that X-ray evidence of sacroiliitis is a late feature of the disease. Computed tomography and magnetic resonance imaging (MRI) can detect AS lesions earlier and with greater consistency than plain radiography, but these methods are not routinely employed due to poor resource settings. MRI enables the detection of approximately 75% more cases of early sacroiliitis that would otherwise have been missed by plain radiography. New therapies such as the tumor necrosis factor (TNF) inhibitors have transformed the treatment paradigm in AS, especially for those patients with aggressive disease. Thus, the development of clinical methods to assess response to therapy has become a priority. This study focuses on measuring the degree of disease activity, job retention, and morbidity in patients with AS in outpatient settings, and monitoring the response to treatment with nonsteroidal anti-inflammatory drugs (NSAIDS), Disease-modifying antirheumatic drugs (DMARDS), and TNF inhibitors, to achieve remission and quality of life.

Objectives

1. To study the clinical profile, diagnosis, management, and time to achieve remission of patients with SpA and long-term follow-up with disease activity indices
2. To assess the outcome of patients on biosimilars in the treatment of ankylosing spondylitis.

Methodology

This was a prospective study of patients with inflammatory back pain due to ankylosing spondylitis. Prior approval from Institutional Ethical Committee was obtained Vide. VMCIEC/03/2017 dated April 04, 2017.

Inclusion criteria

All consecutive patients who had inflammatory back pain and diagnosed to have SpA by ASAS criteria (Assessment of SpA International society)[4] were included in this prospective study in two different centers' of Rheumatology over 2 1/2 year period (recruitment 18 months and follow up for 12 months). We started from April 2017 and completed by December 2019. Clinical assessment was made by the rheumatologist following ASAS criteria.

Exclusion

All patients who were pregnant, who were living far, who had degenerative disc disease and TB spine.

After obtaining informed consent, clinical characteristics, bloods-erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), disease activity using Bath Ankylosing spondylitis disease activity index and functional index (BASDAI, BASFI), and drug treatment were entered on to the data collection proforma. MRI Imaging of spine and sacroiliac joint (SIJ) (STIR sequences) was used in this study during the first visit for identifying inflammatory changes–sacroiliitis and other features. After the initial assessment, all patients were managed as per BSR (British Society of Rheumatology) guidance. Once diagnosis confirmed, Sulfasalazine was started for most patients, and Methotrexate or Leflunomide was used for patients with peripheral arthritis (risk of developing connective tissue disease if patients positive for ANA take sulfasalazine).

Most patients were started on NSAIDs and intramuscular methylprednisolone 80 mg or prednisolone 10 mg orally daily for 1 week.

During the review consultation, patients were offered treatment escalation - second line DMARDS, TNF blockers etc. after BASDAI and BASFI scores as per BSR guidelines.[5] Prebiologic screening with chest X-ray, bloods, viral serology, and counseling was done. Patients were reviewed every 3 months and compliance to the protocol was stressed. The response to treatment was assessed and compared with other studies.

Statistical analysis

The data were analyzed using SPSS 23.0 version (Statistical package for the social sciences version 23.0) by IBM and in year 2015. and variance was found using analysis of variance tool for repeated measures. $P < 0.05$ was considered to be statistically significant.

Results

We enrolled 57 patients, but 15 patients were excluded due to attrition-(who lost to follow up or were <3 months of follow-up). Out of 42 patients, 37 were male and 5 were female (7.4: 1-M: F) with a mean age of 33.5 years.

These patients presented with back pain, stiff back, for weeks to months, unable to squat or bend forward and and also driving difficulties due to neck pain. Eight patients reported buttock pain. Patients also presented with knee and ankle synovitis. Sleep was affected and had morning stiffness too.

All had the diagnosis of SpA under ASAS criteria, MRI spine and SIJ showing evidence of inflammation. MRI imaging included lumbar spine, SIJ STIR images, and disc changes were reviewed. Marrow edema, vertebral corner lesions

and fatty lesions, spinal ligament ossifications scored in favour of ankylosing spondylitis. The changes in patients who had degenerative changes like osteophytes, disc dehydration were insignificant.

HLA B27 antigen was positive in 11 (out of 19 patients in whom the test was done) using the polymerase chain reaction (PCR) method. Raised ESR was present in 24 out of 42 patients, while CRP was elevated in 17 out of 42 patients. Mean scores are depicted in Table 1. BASDAI and BASFI scores were recorded at the time of diagnosis, 4 weeks, 12 weeks 24 weeks, 52 weeks, and 2 years, and have shown improvement as in Tables 2 and 3.

Table 1: Demographic and disease characteristics

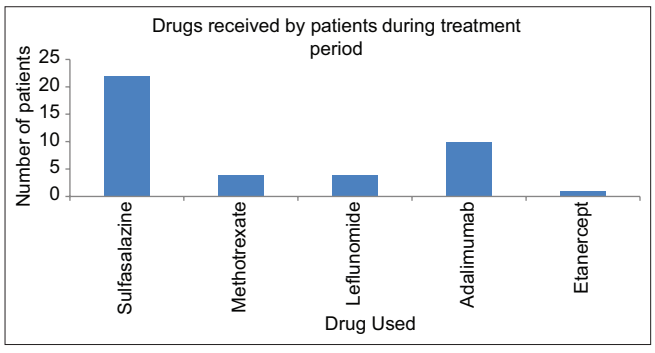
	Number of patients	Mean	Range
Age		33.48	18-61 years
Sex	5-female, 37-male		
Duration		41 months	1 week-10 years
Spinal disease	(42)		
Peripheral	22		
Iridocyclitis	3		
HLA-B27	11/19 positive		
ESR	24/42	26.4	2.5-110 mm
CRP	17/42	14	0.9-91 mg/dl

All patients had Intramuscular injection of methylprednisolone 80 mg as induction therapy. ESR: Erythrocyte sedimentation rate, CRP: C reactive protein

Table 2: Statistical analysis of bath ankylosing spondylitis functional index scores during the treatment course

(BASFI)	Weeks	Mean	SD	*P*
BASFI	0	5.08	2.318	0.001**
BASFI	4	3.32	1.94	
BASFI	12	3.31	1.969	
BASFI	24	2.45	0.772	
BASFI	52	2.50	1.671	
BASFI	104	2.07	1.599	

***P* (<0.05) is statistically significant. BASFI: Bath ankylosing spondylitis functional index, SD: Standard deviation



Graph 1: Bar chart depicting the number of patients on Disease-Modifying AntiRheumatic Drugs and Biosimilars

NSAIDS were used at the time of diagnosis and during subsequent visits, conventional DMARDs and Biosimilar anti TNF drugs were used to treat these patients. Sulfasalazine was the drug used in 22 patients while Methotrexate and Leflunomide were used in four each [Graph 1]. Second DMARDs were used for patients who either failed or had intolerance to first-line drugs. Ten patients used Adalimumab biosimilar drug and one patient used etanercept. Those patients who had bio DMARDS used minimal NSAIDs and no steroids and no flares.

Criteria for remission included BASDAI score less than or equal to 2, BASFI score <2.4, absence of active arthritis or enthesitis or extra-articular manifestations in the last 6 months.[6]

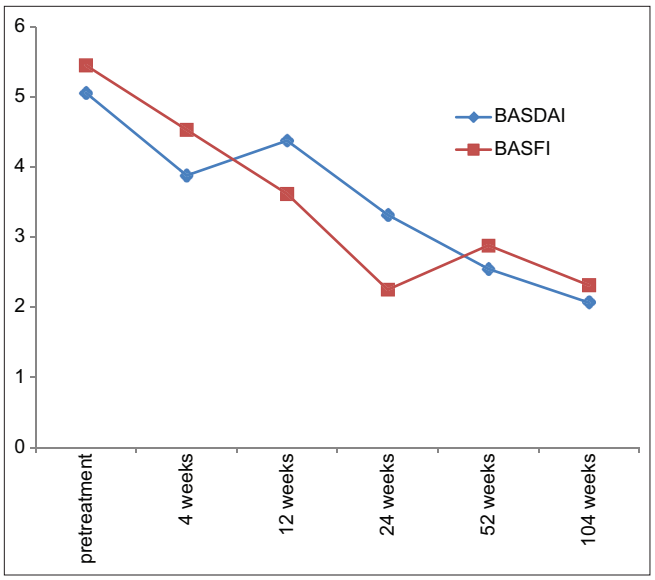
Our results show that by 24 weeks, most patients achieve remission with mean BASDAI 2.26(SD-0.701) and mean BASFI 2.45 (SD-0.772). at the end of 2 years mean BASDAI 2.33 (SD-1.817) and mean BASFI 2.07 (SD -1.599). both were statistically significant [Graph 2].

Extra-articular manifestations including uveitis, dactylitis, iridocyclitis, and heel pain (plantar fascitis) were observed in 22 patients. The most common site of enthesitis was plantar fasciitis.

Use of biosimilars

Eleven out of 42 needed Biosimilars and adalimumab was used for 10 patients. Etanercept was used for one. Two patients are continuing on biosimilar injections for 4 years now and others on an average have used 4–6 doses.

Table 4 illustrates that mean disease activity was high at diagnosis and biosimilar drugs were added to oral DMARDS at 12 weeks and since 24 weeks, they have maintained remission until 104 weeks. Disease remission rate and job



Graph 2: Graph showing bath ankylosing spondylitis disease activity index and bath ankylosing spondylitis functional index indices showing downward trend and achieving remission by 24 weeks and maintained for 104 weeks

Table 3: Statistical analysis of bath ankylosing spondylitis disease activity index scores over the treatment course

	Weeks	Mean	SD	*P*
BASDAI	0	5.37	2.364	0.001**
BASDAI	4	3.65	2.202	
BASDAI	12	3.57	2.199	
BASDAI	24	2.26	0.701	
BASDAI	52	2.90	1.885	
BASDAI	104	2.33	1.817	

***P* (<0.05) is statistically significant. BASDAI: Bath ankylosing spondylitis disease activity index, SD: Standard deviation

Table 4: Mean disease indices for patients on biosimilars

Mean	0 weeks	4 weeks	12 weeks	24 weeks	52 weeks	104 weeks
BASFI	5.6	3.4	4.34	2.2	2.5	1.7
BASDAI	4.85	3.63	3.7	1.7	2.47	1.74

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index

retention were high in our study with 81% in work with a mean follow-up of 1 year.

Discussion

Spondyloarthropathy involves the spine, SIJ and peripheral joints and also associated with extra-articular manifestations such as uveitis, iritis, psoriasis, enthesitis, and inflammatory bowel disease. Out of the 57 patients diagnosed with AS and enrolled for the study the male-to-female ratio was about 7:1 in contrast to trends suggested by Agarwal and Malaviya[2] and other studies.[1,3] All females presented in their early thirties while males had their presentations in mid-twenties suggesting an early onset of the disease among the males. It could also be because women tend to disregard back pain as simple and use conservative treatment.

The impact of the inflammatory disease can be variable resulting in chronic pain and debility hence early diagnosis and treatment are important. Serum biomarkers have been used in assessing disease activity, treatment response, and as predictors of radiographic severity.[6,7] We found that elevated ESR, CRP were seen in about 57% of patients with AS, with mean ESR 26.4 mm and CRP 14 mg/dl, implying inflammatory activity was present.[8] 19 patients had tested for HLA B27 antigen using the PCR method, (cost issues). 11 were found to be positive. PCR method was used. 11/19 (57%) positivity for HLA B27 suggests low positive rate however 43% patients couldnt test due to high cost. HLA B27 positivity is associated with more severe disease clinically and radiographically.[9] Haridas *et al*. study showed positivity in 21% in south Indian population while B27 alleles showed more than 70% positivity.[10]

MRI is being used increasingly to diagnose radiographic AS while a separate group of patients have been classified as nonradiographic AS.[7] All study patients had MRI spine and SIJ with 72% showing bilateral sacroiliitis and hip joint effusion. Five patients had ankylosed spine and bony sclerosis of SIJ which suggests the chronic nature of this disease. Other inflammatory changes reported include supraspinalis tendonitis, cervical facet joint edema, and atlanto-occipital joint space narrowing, and extraskeletal presentations such as dactylitis, uveitis, patellar bursitis, and trochanteric bursitis. The presence of syndesmophytes, male sex, HLA B27 positivity, high CRP, and smoking have been identified as strong risk factors for radiological damage.[11]

The functional index (BASFI) and the subjective activity index (BASDAI) are strongly inter-correlated when assessing AS severity, both by their absolute values and by the Ankylosing Spondylitis Disease Activity Score.[12,13]

Our results show, that, by 24 weeks, all patients achieve remission with mean BASDAI 2.26 (SD-0.701) and mean BASFI 2.45 (SD-0.772). At the end of 2 years, mean BASDAI 2.33,(SD-1.817). mean BASFI 2.07 (SD-1.599), both these indices were statistically significant ($P < 0.001$). This is comparable to 2009 study done by Agarwal and Malaviya.[2]

Before the advent of biologic agents, treatment for AS was limited to using NSAIDS and DMARDS like sulfasalazine. Toward the end of the 20th century, TNF-α was found to be overexpressed in the SIJ tissues in patients with Ankylosing Spondylitis.[14] Since 2003, biologic drugs have been licensed to use in patients with SpA. Currently, there are six biological agents approved for use in Ankylosing Spondylitis, including five monoclonal antibodies (i.e., infliximab, adalimumab, certolizumab pegol, golimumab, and secukinumab) and a soluble TNF receptor, etanercept. These drugs and their biosimilar agents have transformed the treatment paradigm in AS, especially for those with aggressive disease and associated extra-articular manifestations.[15]

Though the biologicals have been effective in patients with Ankylosing Spondylitis, their high cost is the major hindrance for their use in majority of Indian patients who have to shell out from their pocket. This had been highlighted by Singhal and colleagues showing many Asian Indian patients with ASpA were deprived of the benefits of these agents.[16] Hence, biosimilar drugs were used and are increasingly being accepted across the world not only for ankylosing spondylitis but also in other conditions.

In our study, we followed multidisciplinary approach for management that included counseling, physiotherapy, NSAIDS, DMARD, intramuscular steroids, and biosimilars. Ten patients were on Adalimumab and 1 patient was on Etanercept. Patients who were on biosimilars showed a reduction in their disease activity in all except one (10/11)

and achieved remission in 4 months to 6 months during the follow-up while they continued on DMARDs and physiotherapy. This was similar to Bruner *et al*. l in 2014.[17] One patient had undergone total hip replacement in our study. One patient was drug free after 4 cycles of biosimilar therapy. Recent insights into the immune mediators of the inflammatory cascade have resulted in targeted treatment strategies in patients with SpAs. Castillo-Gallego *et al*. have thrown more light on the bioDMARDS including Interleukin (IL)-17 blockers, and IL-22 monoclonal antibodies in achieving effective disease control and remission in patients with SpAs.[18]

The extra articular features like uveitis and enthesitis responded to DMARDs and topical eye preparations. It may be possible that inflammatory bowel disease was not found in this cohort due to early aggressive therapy for ankylosing spondylitis and achieve remission. With the advent of various immune cytokine blockers the clinicians are able to give good quality of care and QoL to the patients.[19]

Patients who can continue their work and maintain their economic activities were supported for job retention. Our follow-up consultations suggested that patients were able to retain their job and were satisfied. Disease remission and job retention were high in our study with 81% in work with a mean follow-up of 1 year.

This study shows the real-world data on spondyloarthritis over 2 years, with tight control of disease activity despite social, financial, and physical impediments. Better communication with patients and family by the team of doctors and nurses might have helped to achieve this and continued follow-up and using low-cost DMARDS in SpA would be an effective strategy and tool for further research in developing countries.

Limitations

First is the limited study population so we cannot make generalizations. Affordability was the reason for the low rate of testing of the HLA B27 antigen. Second, biologics and biosimilars usage has been restricted due to financial constraints. Follow-up imaging might have added more value in reinforcing the remission. Third, the dose of NSAIDS could have helped to analyze the long-term implications. Monitoring of inflammatory mediators could also have helped to assess the duration to achieve biochemical remission along with BASDAI and BASFI.

Within these limitations, our patients responded reasonably well to the strategies employed and managed to work and adopt work-life balance and keep productivity.

Conclusion

SpA is increasing in incidence and patients still reach the specialists late (average of 25 months after the onset of symptoms) and have a reduced quality of life and loss of productivity due to work disability and sickness absenteeism. NSAIDS and DMARDS work well, however, Biosimilars do have a role in selected patients. Remission is good and job retention is high in our cohort with good quality of life. This study shows the real-world data on SpA, with tight control of disease activity despite social, financial, and physical impediments. Using low-cost DMARDs in SpA and diagnosis using MRI at the start for diagnosis would have contributed to effective control of arthritis in SpA and further research is warranted in developing countries.

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Conflicts of interest

There are no conflicts of interest.

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RESEARCH LETTER | VOLUME 19, ISSUE 12, P2027-2029, DECEMBER 01, 2022

Masked right bundle branch conduction delay pattern during left bundle branch pacing

Pugazhendhi Vijayaraman, MD • Shunmuga Sundaram Ponnusamy, MD

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The specific criteria for left bundle branch pacing (LBBP) include right bundle branch delay (RBBD) pattern (qR/Qr/rSR') in lead V_1 and transition from nonselective to selective left bundle branch (LBB)– or left ventricular septal (LVS)–only capture at near-threshold outputs.[1] An absent RBBD pattern during deep septal pacing would generally indicate that the pacing lead has not reached the LBB/LVS and requires additional rotations. Rarely the qR/Qr/rSR' pattern in lead V_1 may be masked (QS pattern) despite LBBP (Figures 1A and 1B , blue circles). The aim of our study was to describe the incidence and mechanisms of the masked RBBD pattern during nonselective LBB capture.

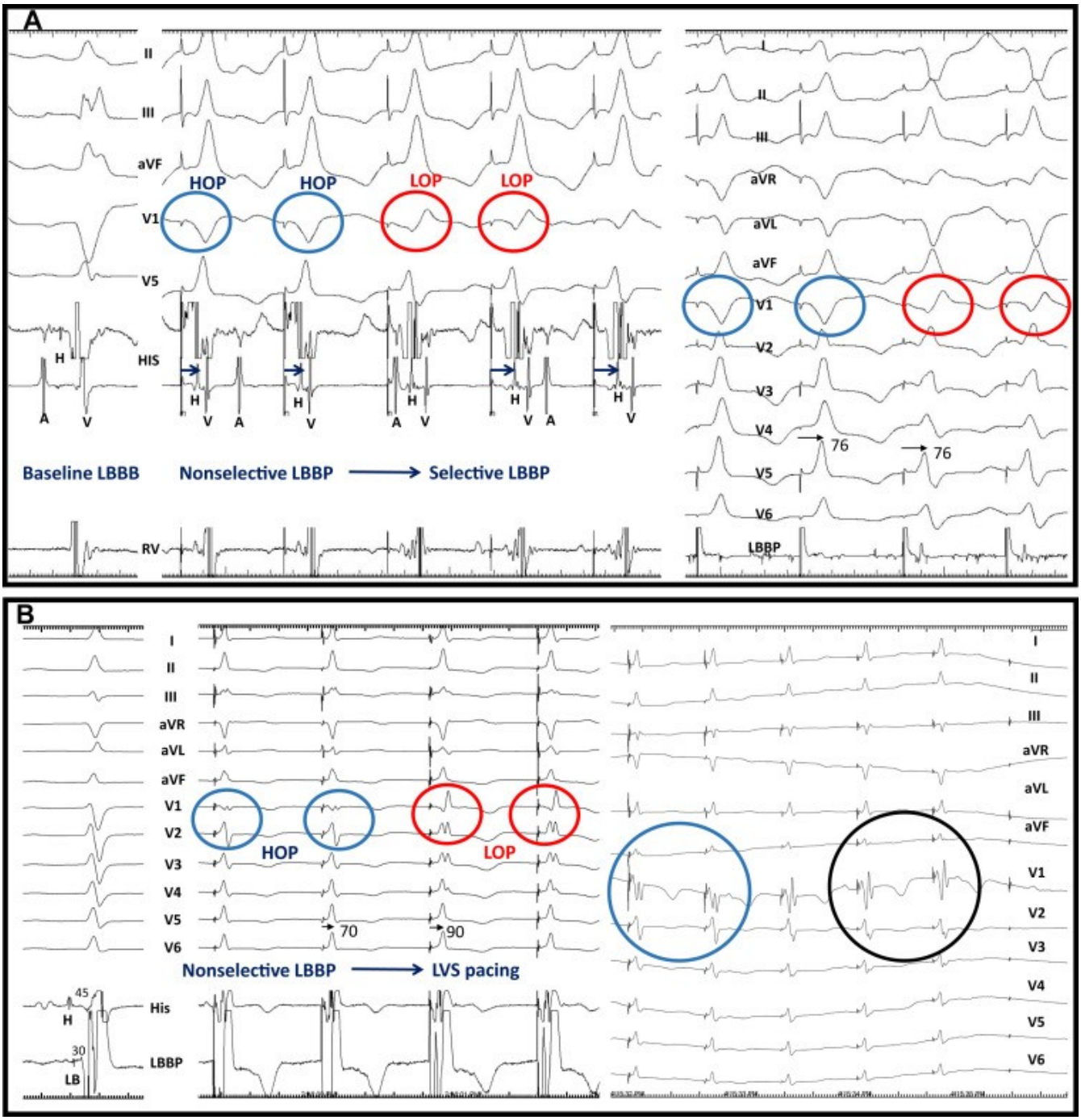

Figure 1 Masked RBBD pattern during nonselective LBBP. A: During HOP to LOP, the QS pattern in lead V_1 transitions to the qR pattern in lead V_1 without change in RWPT in leads V_5 and V_6, consistent with nonselective (*blue circle*) to selective (*red circle*) LBB capture. Note the corresponding change in stimulus-His intervals. **B:** During HOP to LOP, the QS pattern in lead V_1 transitions to the qR pattern in lead V_1 with a longer RWPT in lead V_5–V_6, consistent with nonselective to LV septal capture. During subsequent threshold testing, a transition from nonselective (*blue circle*) to selective LBB capture (*black circle*) without an RBBB pattern in lead V_1 is seen. The LBB-V interval was 30 ms with early activation of RBB during LBBP. HOP = high-output pacing; LBB = left bundle branch; LBBP = left bundle branch pacing; LOP = low-output pacing; LV = left ventricular; LVS = left ventricular ... RBB = right bundle branch; RBBB = right bundle branch block; RBBD = right bundle branch ... RW

R-wave peak time.

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Keywords

Left bundle branch pacing • Right bundle branch block • Left bundle branch capture • Left ventricular septal pacing • Distal His bundle pacing

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Evaluation of Criteria for Left Bundle Branch Capture

Shunmuga Sundaram Ponnusamy, MD • Pugazhendhi Vijayaraman, MD

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Keywords

Left bundle branch pacing • Left ventricular activation time • R-wave peak time • Left bundle branch potential • Conduction system capture

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BRIEF COMMUNICATION

M-beat—A novel marker for selective left bundle branch capture

Shunmuga Sundaram Ponnusamy MD, DM, CEPS, William Basil BE, Pugazhendhi Vijayaraman MD, FHRS

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Abstract

Introduction

Premature-ventricular-complexes (template/fixation beat) guided left bundle branch pacing (LBBP) was recently described as a novel method of successful lead deployment by rapid rotations.

Methods

We aimed at analyzing the incidence of a unique morphology template beat, which we labelled as 'M-beat' in patients undergoing PVC-guided LBBP, its ability to predict selective LBB-capture and clinical significance.

Results

Overall 210 out of 217 attempted-patients (96.7%) underwent successful LBBP. Template beat was noted in 90.4% patients (n = 190) and M-beat in 32.8%(n = 69). Non-selective to selective capture transition demonstrated in 55.2%(n = 116). The QRS duration of the M-beat was 129.3 ± 13.1ms. Patients were divided into two groups: Group-I with M-beat (n = 69;32.8%) and Group-II without M-beat (n = 141; 67.2%). The mean fluoroscopy-time was significantly less in group-I as compared to group-II (13.1 ± 11.1 vs 16.8 ± 12.04 minutes; p–0.03). Patients in group-II required more attempts as compared to group-I for successful lead deployment (2.8 ± 1.09 vs 2.2 ± 1.04; p – 0.01). Six patients showed loss of R-wave in lead-V1 and 2 showed rise in LBB capture threshold by >1V during follow-up in group-II. M-beat had a specificity of 96.77% and sensitivity of 58.62% (positive-predictive-value-98.55%) to predict selective-LBB capture. Myocardial excitability would not modify the occurrence of M-beat as opposed to capture transition response since it could be demonstrated without pacing protocols. When confirmation of LBB-capture itself would

be difficult in patients with baseline LBBB-morphology, M-beat with 42.8% incidence predicted selective capture with 96.7% specificity and 66.04% sensitivity(positive-predictive-value-97.22%).

Conclusion

M-beat is a marker of transient-selective LBB-capture, independent of the local myocardial excitability with high specificity and positive predictive value irrespective of the baseline QRS morphology.

CLINICAL DEVICE | VOLUME 19, ISSUE 8, P1272-1280, AUGUST 01, 2022

Rescue left bundle branch area pacing in coronary venous lead failure or nonresponse to biventricular pacing: Results from International LBBAP Collaborative Study Group

Pugazhendhi Vijayaraman, MD, FHRS • Bengt Herweg, MD, FHRS • Atul Verma, MD, FHRS • ... Weijian Huang, MD, FHRS • Marek Jastrzebski, MD, PhD • Kenneth A. Ellenbogen, MD, FHRS •

Show all authors

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Background

Cardiac resynchronization therapy (CRT) using biventricular pacing (BVP) is effective in patients with heart failure, left bundle branch block (LBBB), and reduced left ventricular function. Left bundle branch area pacing (LBBAP) has been reported as an alternative option for CRT.

Objective

The purpose of this study was to assess the feasibility and outcomes of LBBAP in patients who failed conventional BVP because of coronary venous (CV) lead complications or who were nonresponders to BVP.

Methods

At 16 international centers, LBBAP was attempted in patients with conventional CRT indication who failed BVP because of CV lead complications or lack of therapeutic response to BVP. Heart failure hospitalization (HFH) and death, echocardiographic outcomes, procedural data, pacing parameters, and lead complications including CV lead failure are ed.

Results

LBBAP was successfully performed in 200 patients (CV lead failures 156; nonresponders 44) (age 68 ± 11 years; female 35%; LBBB 55%; right ventricular pacing 23%; ischemic cardiomyopathy 28%; nonischemic cardiomyopathy 63%; left ventricular ejection fraction [LVEF] ≤35% in 80%). Procedural duration was 119.5 ± 59.6 minutes, and fluoroscopy duration was 25.7 ± 18.5 minutes. LBBAP threshold and R-wave amplitudes were 0.68 ± 0.35 V @ 0.45 ms and 10.4 ± 5 mV at implant, respectively, and remained stable during mean follow-up of 12 ± 10.1 months. LBBAP resulted in significant QRS narrowing from 170 ± 28 ms to 139 ± 25 ms (P <.001) with V_6 R-wave peak times of 85 ± 17 ms. LVEF improved from 29% ± 10% at baseline to 40% ± 12% (P <.001) during follow-up. The risk of death or HFH was lower in those with CV lead failure than in nonresponders (hazard ratio 0.357; 95% confidence interval 0.168–0.756; P = .007)

Conclusion

LBBAP is a viable alternative to CRT in patients who failed conventional BVP due to CV lead failure or who were nonresponders.

Graphical abstract

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Keywords

Biventricular pacing failure • Cardiac resynchronization therapy • Heart failure • Left bundle branch area pacing • Nonresponder

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Images and Vignettes in Clinical Electrophysiology

Left Bundle Branch Optimized Cardiac Resynchronization Therapy in Mesocardia With Bilateral Superior Vena Cava

Shunmuga Sundaram Ponnusamy MD, DM [a], Thabish Syed MBBS, DNB [a], William Basil BE [b]

https://doi.org/10.1016/j.jacep.2021.09.005

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Keywords

bilateral superior vena cava; left bundle branch optimized cardiac resynchronization therapy; left bundle branch pacing, mesocardia; right-sided left bundle branch pacing

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IMAGES AND VIGNETTES IN CLINICAL ELECTROPHYSIOLOGY

Left Bundle Branch Optimized Cardiac Resynchronization Therapy in Mesocardia With Bilateral Superior Vena Cava

Shunmuga Sundaram Ponnusamy, MD, DM,[a] Thabish Syed, MBBS, DNB,[a] William Basil, BE[b]

A 52-year-old woman was admitted for the management of nonischemic cardiomyopathy, left bundle branch block (QRS duration, 174 ms) with left ventricular (LV) ejection fraction of 25%. Further evaluation showed mesocardia, midline septum, bilateral superior vena cava (SVC) with dilated coronary sinus (Figure 1A). Cardiac magnetic resonance showed no evidence of scar as demonstrated by absent late gadolinium enhancement. Left bundle branch pacing (LBBP) was performed from the right side using C315 sheath and 3830 SelectSecure lead (Medtronic) by premature ventricular complex-guided approach (1). Although meant for left-sided deployment, the C315 sheath could be placed easily in the interventricular septum 1.5 cm below the tricuspid leaflet without reshaping the sheath curvature by gently withdrawing it from the right ventricular apex. Deep septal deployment in the left bundle branch area beneath the LV subendocardium (Figure 1B) resulted in partial correction with residual conduction delay (peak LV activation time, 108 ms at 10V and 2V-pacing output; paced QRS duration, 140 ms, unipolar-pacing threshold 0.5 V at 0.5 ms pulse width) (Figure 1C). Hence, coronary sinus was cannulated and an active fixation LV lead was placed using a subselection catheter in the posterolateral vein (Figure 1A). Left bundle branch optimized cardiac resynchronization therapy (LOT-CRT) through the right SVC reduced the QRS duration to 118 ms with normal QRS axis (+90°) (Figure 1C, Video 1). Computed tomographic imaging with 3-dimensional reconstruction showed mesocardia, midline septum, and LBBP lead tip in the LV subendocardium without penetrating into the cavity (Figure 1B). The patient showed symptomatic improvement with increase in LV ejection fraction to 37% at the end of 1 month. LOT-CRT provides greater electrical resynchronization as compared to biventricular pacing and could be considered as an alternative strategy, especially in patients with suboptimal results from biventricular pacing (2). Right-sided LOT-CRT can be safely performed with the fixed curve C315 sheath to achieve a better resynchronization therapy in patients with difficult left-sided entry.

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Response of functional mitral regurgitation in nonischemic cardiomyopathy to left bundle branch pacing

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Background

Functional mitral regurgitation (FMR) in patients with cardiomyopathy is correlated with morbidity and mortality in heart failure. The response of FMR to cardiac resynchronization therapy (CRT) varies.

Objectives

The purpose of this study was to analyze the incidence and severity of FMR in patients with nonischemic cardiomyopathy (NICM) and left bundle branch block (LBBB) and the response to left bundle branch pacing (LBBP).

Methods

Patients who had undergone LBBP for NICM, LBBB, and FMR between 2019 to 2021 were included retrospectively in the study.

Results

A total of 79 patients were identified, of whom 6 were excluded (5 no consistent LBB capture, 1 prosthetic mitral valve). The remaining 73 patients were divided into 2 groups based on the y of FMR into group I with mild FMR (n = 35 [48%]) and group II with sign FM 2%]). Mean follow-up duration was comparable in both groups. Group II v

characterized by higher N-terminal pro–brain natriuretic peptide levels, New York Heart Association functional class, and larger left ventricular dimensions. LBBP resulted in significant reduction in QRS duration in both group I (113.8 ± 12.7 ms; *P* <.0001) and group II (117.3 ± 10.3 m s; *P* <.0001). LBBP resulted in similar percentage reduction in QRS duration (–31% ± 10% vs –33% ± 8%; *P* = .34), left ventricular (LV) end-diastolic diameter (–8% ± 10% vs –11% ± 12%; *P* = .25), LV end-diastolic volume (–26% ± 12% vs –31% ± 27%; *P* = .31), and LV end-systolic volume (–39% ± 16% vs –37% ± 30%; *P* = .72) in groups I and II, respectively. Percentage change (+59% ± 39% vs +59% ± 41%; *P* = 1) and absolute change (+19.9% ± 10.4% vs +17% ± 10.04%; *P* = .22) in LV ejection fraction were similar in both groups. In group II, 31 patients (82%) showed significant reduction in FMR severity during follow-up. No patients in group I showed worsening of FMR.

Conclusion

LBBP resulted in excellent electrical resynchronization with significant reduction in FMR severity in the majority of patients with significant FMR and no worsening of FMR from baseline in any patient.

Graphical abstract

Figure thumbnail fx1

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Keywords

Cardiac resynchronization therapy • Functional mitral regurgitation • Heart failure • Left bundle branch block • Left bundle branch pacing • Nonischemic cardiomyopathy

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How to rebuild a damaged heart: The role of left bundle branch pacing to reduce functional mitral regurgitation

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Electrophysiological characteristics of septal perforation during left bundle branch pacing

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BACKGROUND Left bundle branch pacing (LBBP) provides a low and stable threshold by direct capture of left bundle fibers on the left ventricular subendocardium. As the procedure involves the deployment of the pacing lead deep inside the septum, septal perforation is a potential complication.

OBJECTIVES The purpose of this study was to analyze the morphology of intracardiac electrograms and unipolar pacing parameters to identify septal perforation in patients undergoing LBBP.

METHODS Patients who had undergone successful LBBP between January 2020 to November 2021 were retrospectively included in the study.

RESULTS LBBP was attempted in 219 patients and was successful in 212 (96.8% success rate). Septal perforation during lead deployment was identified in 30 patients (14.1%). Peak troponin release was 188 ± 162 pg/mL. Mean unipolar impedance during septal perforation was 404.6 ± 19.9 Ω (400–450 Ω in 16 patients [53.3%]; <400 Ω in 14 patients [46.7%]). A cutoff <450 Ω for diagnosing septal perforation had high sensitivity (100%) and specificity (96.6%). Current of injury amplitude reduced from 15.4 ± 11.6 mV just before perforation to 0.9 ± 0.6 mV after perforation. Based on morphology, unfiltered unipolar electrograms were classified into 2 patterns: (1) type I (QS) seen in 20 patients (67%) due to complete perforation (mean unipolar impedance 402.5 ± 20.4 Ω); and (2) type II (RS/rS) seen in 10 patients (33%) due to partial perforation, with 80% showing capture (mean impedance 411 ± 21.3 Ω). All 30 patients underwent successful reimplantation at a new site. No patient developed lead dislodgment during mean follow-up of 9.9 ± 6.7 months.

CONCLUSION Although considered one of the concerns of LBBP, septal perforation, when recognized promptly during implantation by unipolar parameters and treated by reimplantation, would be benign and not associated with an unfavorable outcome.

KEYWORDS Current of injury; Left bundle branch pacing; Pacing impedance; Septal perforation; Template beat; Unfiltered unipolar electrogram

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Introduction

His-Purkinje conduction system pacing aims to directly capture the cardiac conduction system, resulting in synchronized activation of the ventricles with the goal of preventing right ventricular (RV) pacing–induced cardiomyopathy.[1–3] Permanent His-bundle pacing (HBP) has been shown to reduce the risk of heart failure hospitalizations, atrial arrhythmias, and mortality compared to conventional RV pacing.[4] However, HBP is associated with variable procedural success rates (65%–92%),[3,5,6] late rise in capture threshold, and increased risk of lead revisions. Since the original report by Huang et al[7] of deep septal left bundle branch pacing (LBBP) to overcome the limitations of HBP, LBBP has gained significant momentum in the last few years.[8–11] Several multicenter observational studies have demonstrated the feasibility and efficacy of LBBP as an alternative to cardiac resynchronization therapy (CRT).[12–14]

Early observations suggest that confirmation of left bundle branch (LBB) capture is essential to achieve maximal electrical resynchronization in patients with heart failure.[14] The left bundle and its branches spread in a fanlike pattern on the left ventricular (LV) septal subendocardium.[15] Successful LBBP lead placement and capture of the LBB involve deployment of the lead in the LV subendocardium. During lead implantation, there is a potential risk of perforation into the LV cavity. Recognizing the septal perforation (SP) during implantation is essential to avoid long-term thromboembolic complications and has to be managed immediately by repositioning the lead at a different site. A drop in unipolar impedance to <500 Ω, sudden rise in capture threshold, and

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loss of myocardial current of injury (COI) are considered markers of SP.[15,16] The morphology of intracardiac electrograms and unipolar pacing impedance during SP have not been well studied. The aim of our study was to analyze the morphology of intracardiac electrograms and unipolar impedances to identify SP in patients undergoing LBBP.

Methods

This retrospective, single-center, observational study included consecutive patients who underwent successful LBBP for symptomatic bradyarrhythmia or as an alternative to CRT between January 2020 and November 2021 (Figure 1). Patients in whom definite LBB capture could not be confirmed were excluded. The study was approved by the Institutional Review Board of Velammal Medical College Hospital and Research Institute and adhered to the guidelines of the Helsinki Declaration. All patients provided informed consent after understanding the nonstandard nature of the procedure. LBBP was performed using C315 sheath and 3830 SelectSecure™ lead (Medtronic Inc., Minneapolis, MN) by deploying the lead 1–1.5 cm below the His bundle along an imaginary line connecting the distal His signal to the RV apex.[15] Continuous monitoring of intracardiac electrograms were done using the Workmate Claris (Abbott, Plymouth, MN) electrophysiology system. The pacing lead electrogram was recorded simultaneously by the electrophysiology recording system and pacing system analyzer.

Pacing lead tip was connected in unipolar configuration with high- and low-pass filter settings of 0.5 and 500 Hz, respectively, to obtain unfiltered electrogram (LB-U) for monitoring the COI. Filtered unipolar electrogram (LB-F) was obtained with high- and low-pass filter settings of 30 and 300 Hz, respectively, to record the LB potential. Notch filtering was done at 50 Hz. Capture of the LBB was confirmed by the presence of right bundle branch conduction delay pattern (qR/rSR in lead V_1) along with demonstration of LBB potential, abrupt shortening and then short and constant peak LV activation time in lead V_6, nonselective to selective/nonselective to septal capture transition, programmed deep septal stimulation,[17] physiology-based electrocardiographic criteria,[18] or V_6–V_1 interpeak interval.[19] SP during lead implantation was identified by unipolar pacing impedance $<500\ \Omega$, associated with abrupt increase in capture threshold and loss of COI in the unfiltered electrograms.[15,16] Once perforation was identified, the lead was gently withdrawn while monitoring unipolar electrograms to demonstrate recovery of myocardial COI, thereby confirming perforation (Figure 2). Bipolar pacing parameters were not used to identify SP. The lead then would be repositioned at a different site to complete the procedure rather than just withdrawing it back, which might predispose to lead dislodgment during follow-up.

Data collection

Baseline characteristics of the study population and indication for pacing were collected. Pacing parameters at the time of implantation and electrocardiographic parameters were documented. If SP was identified, the unfiltered unipolar lead electrogram and the unipolar pacing impedance were recorded. The morphology of the unfiltered unipolar lead electrogram at the site of perforation was analyzed. Pacing parameters after successful repositioning of the lead were recorded. Echocardiography was performed before and after the procedure to assess septal thickness, LV systolic function, valvular regurgitation, and depth of the lead inside the septum. Serum high-sensitivity cardiac troponin I measurement was done at baseline and 12 hours after the procedure. Patients underwent follow-up in the device clinic at 15 days, 1 month, and every 3 months thereafter.

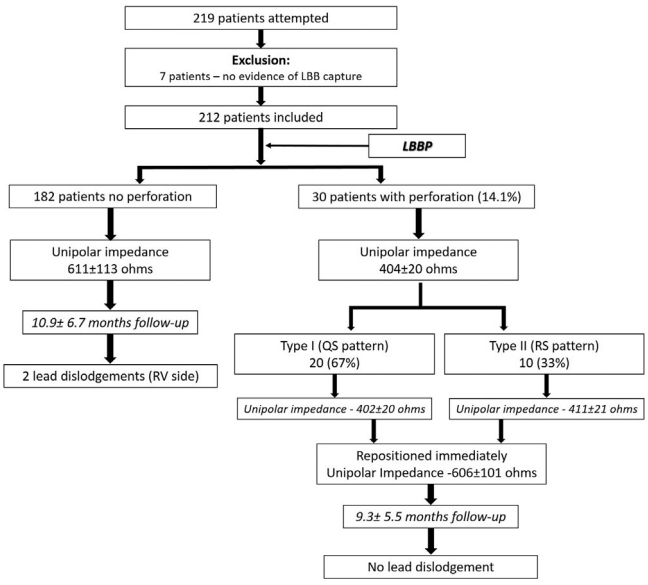

Figure 1 Flow chart of the study population. Septal perforation was noted in 14.1% of the patients. Two different patterns of unfiltered unipolar electrograms were observed based on complete or partial perforation. LBB = left bundle branch; LBBP = left bundle branch pacing; RV = right ventricle.

Statistical analysis

Categorical variables are given as frequency (percentage) and compared with the χ^2 test. Continuous variables are given mean ± SD and were compared with the Student *t* test. Statistical analysis was performed using SPSS Version 25 (SPSS, Chicago, IL). $P < .05$ was considered significant.

Results

Baseline characteristics

LBBP was attempted in 219 patients using the C315 sheath and 3830 SelectSecure lead. The pacing lead has an open helix (1.8 mm in length) as the cathode and a radiopaque anode separated by 9 mm. LBBP was successful in 212 patients (96.8% acute procedural success rate). LBB capture could not be confirmed in the remaining 7 patients, who were excluded from the study. SP during lead deployment was identified in 30 patients (14.1%) (Table 1). The indications for pacing were symptomatic sinus node dysfunction (n =

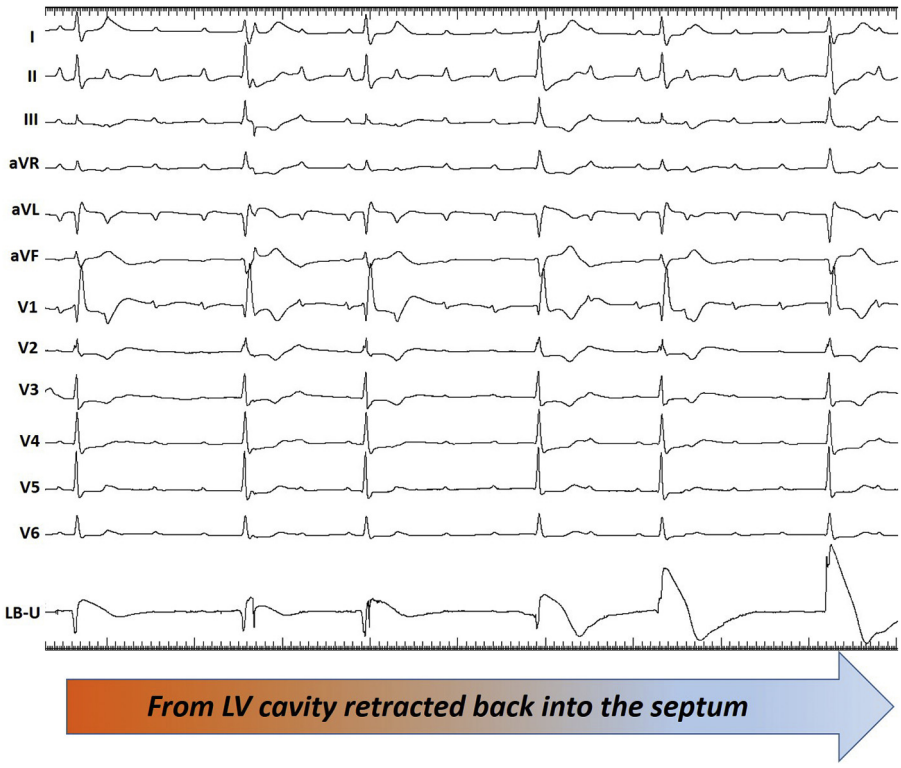

Figure 2 Reappearance of current of injury in the unfiltered unipolar electrogram as the lead was retracted back from the left ventricular (LV) cavity into the septum.

2), atrioventricular block (n = 14), as an alternative to CRT (n = 13), and atrioventricular junction ablation (n = 1). Patients were asymptomatic for SP during implantation. Mean fluoroscopy duration for the procedure was 16.3 ± 4.7 minutes. Mean duration of follow-up was 10 ± 7 months. Mean age of the patients who had SP was similar to those without SP (60.1 ± 11.2 years vs 62.3 ± 11.3 years, respectively; $P = .32$). There was no difference between patients who had SP compared to those without SP with regard to interventricular septal thickness (10.1 ± 1.6 mm vs 10.5 ± 1.4 mm; $P = .15$) and LV ejection fraction (44.1% ± 16.2% vs 47.8 ± 15.7%; $P = .23$).

Unipolar pacing impedance

Mean unipolar pacing impedance during SP was 404.6 ± 19.9 Ω (range 360–440 Ω) (n = 30). Pacing impedance between 400 and 450 Ω was noted in 16 patients (53.3%) and <400 Ω in the remaining 14 patients (46.7%). Mean unipolar pacing impedance of patients without SP was 612.1 ± 113.2 Ω (n = 182). In this group, pacing impedance between 450 and 500 Ω was noted in 18 patients (9.9%), 400–450 Ω in 5 patients (2.7%), and ≤400 Ω in 1 patient (0.5%). For identification of SP, a cutoff <500 Ω had high sensitivity (100%) but low specificity (86.6%). Similarly, a cutoff <400 Ω had high specificity (99.4%) and low sensitivity (46.6%). A cutoff <450 Ω would be an optimal value as it has sensitivity of 100%, specificity of 96.6%, positive predictive value of 83.3%, and negative predictive value of 100% (Table 2). Serial monitoring of COI during lead deployment showed significant drop in amplitude from 15.4 ± 11.6 mV just before perforation to 0.9 ± 0.6 mV after perforation into the LV cavity. Fifteen patients (50%) had demonstrable capture during perforation, with mean threshold of 3.02 ± 0.7 V (0.5-ms pulse width). R-wave peak time (RWPT) measured in lead V_6 was 75.9 ± 17.3 ms (n = 15) during perforation.

All 30 patients underwent successful repositioning of the lead at a new site. Extreme care was taken to avoid entering the same site, which would predispose to subsequent lead dislodgments. We then utilized the following parameters to confirm a new entry site: (1) fluoroscopic landmark; (2) pace-mapping on the right side of the septum to show change in QRS morphology of inferior leads (R/RS/rS/S pattern) compared to the original site; (3) premature ventricular complexes (template/fixation beats)[20,21] during rapid lead deployment; and (4) movement of lead during deployment in the left anterior oblique fluoroscopic view. Absent template/fixation beats during rapid deployment and hypertransmission of rotations to the lead tip inside the septum would favor a same site and thus was avoided. A different paced QRS morphology in the inferior leads would confirm a new site before deployment. Unipolar pacing impedance after successful lead repositioning was 606.8 ± 101.1 Ω, with capture threshold of 0.4 ± 0.1 V at 0.5-ms pulse width (n = 30). RWPT after reimplantation was less than during perforation, although not statistically significant (n = 15; 71 ± 12.4 ms vs 75.9 ± 17.3 ms; $P = .38$).

Unfiltered unipolar electrogram during perforation

Based on the morphology, unfiltered unipolar electrograms were classified into 2 different patterns: (1) type I (QS

Table 1 Baseline characteristics of patients with septal perforation

Total no. of patients	30
Age (y)	60.1 ± 11.2
Male/female	14/16
Septal thickness (mm)	10.1 ± 1.6
Indication for pacing	
Atrioventricular block	14
CRT alternative	13
Sinus node dysfunction	2
AV junction ablation	1
LBBP fluoroscopy duration (min)	16.3 ± 4.7
QRS duration (ms)	
Baseline	152.1 ± 31.6
Post-LBBP	116.2 ± 11.1
RWPT (ms)	71.1 ± 11.2
LV ejection fraction (%)	
Baseline	45.1 ± 16.1
Follow-up	49.6 ± 14.7
Unipolar impedance (Ω)	
During perforation	404.6 ± 19.9
After repositioning	606.8 ± 101.01
COI amplitude (mV)	
Before perforation	15.4 ± 11.6
During perforation	0.9 ± 0.6
Unipolar pacing threshold (V)	0.4 ± 0.1
Sensed R wave (mV)	6.7 ± 4.1
Peak troponin release (pg/mL)	188 ± 162

Values are given as mean ± SD or n unless otherwise indicated.

AV = atrioventricular; COI = current of injury; CRT = cardiac resynchronization therapy; LBBP = left bundle branch pacing; LV = left ventricle; RWPT = R-wave peak time.

pattern); and (2) type II (RS or rS pattern) (Figure 3). Type I pattern was noted in 20 patients (67%) and was characterized by predominantly negative deflection (QS pattern) with or without notches (Figure 4). As the cathode (helix) of the lead would be placed within the LV cavity away from the septal myocardial depolarization wavefront after perforation, steep negative deflection would be recorded. Mean unipolar pacing impedance was 402.5 ± 20.4 Ω. The amplitude of COI dropped from 12.7 ± 9.3 mV before perforation to 0.9 ± 0.6 mV after perforation. Seven of 20 patients (35%) with type I pattern showed capture of myocardium during perforation, with mean capture threshold of 3.3 ± 0.4 V (0.5-ms pulse width)

Type II pattern was noted in 8 patients (33%) and was characterized by an initial positive deflection without notches (RS pattern). We hypothesize that a subtotal perforation with a small part of the cathode in contact with the septal myocardium as the mechanism of the "RS" pattern. With partial contact, the proximal end of the helix would record an initial positive deflection, followed by a negative deflection ("RS") as the wavefront travels across the septal myocardium (Figure 5). Mean unipolar pacing impedance was 411 ± 21.3 Ω. The amplitude of COI dropped from 19.7 ± 10.5 mV before perforation to 1.3 ± 0.9 mV after perforation. Eight of 10 patients (80%) with type II pattern showed capture of myocardium during perforation, with mean capture threshold of 2.8 ± 0.8 V (0.5-ms pulse width). Due to partial contact, both unipolar pacing impedance and amplitude of COI during perforation were greater in the type II ("RS/rS") pattern group compared to the type I ("QS") pattern group, although not statistically significant (P = .29 and .15, respectively). Similarly, 80% of patients with type II pattern showed capture during perforation compared to 35% with type I pattern (P = .02). Irrespective of the type of perforation pattern, the lead was removed and reimplanted at a different site with good COI. Peak troponin release was 188 ± 162 pg/mL. There were no incidence of coronary artery injury, septal hematoma, or systemic embolism. Postprocedure transthoracic echocardiography showed no evidence of lead perforation or ventricular septal defects. Follow-up echocardiography showed no evidence of residual ventricular septal defect; an increase in LV ejection fraction from 44.1% ± 16.2% to 49.6 ± 14.7%; and a reduction in LV end-diastolic diameter from 54.5 ± 9.8 mm to 51.2 ± 9.2 mm, although not statistically significant (P = .17 and .18, respectively). No patient developed lead dislodgment during mean follow-up of 9.9 ± 6.7 months. Two patients in the group without SP (1.09%; n = 182) during implantation had dislodgment (into RV) requiring repositioning in the LBB area (mean follow-up 10.9 ± 6.7 months).

Discussion

The major findings of our study were as follows. (1) SP with significant drop in COI occurred in 13.9% of patients during LBBP. (2) Two patterns of unfiltered unipolar electrograms (67% QS, 33% RS/rS) due to complete or partial SP were observed. (3) Unipolar pacing impedance <450 Ω predicted SP with sensitivity of 100% and specificity of 96.4%. The procedural technique of LBBP involves deep septal deployment of the lead below the LV subendocardium to capture the left bundle or its branches. The number of rotations required to reach the LBB area varied depending on septal

Table 2 Unipolar pacing impedance cutoff value for diagnosing septal perforation

Impedance cutoff (Ω)	No perforation (n = 182)	Perforation (n = 30)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
<500	24 (13.2)	30 (100)	100	86.6	55.5	100	88.5
<450	6 (3.3)	30 (100)	100	96.6	83.3	100	97.13
<400	1 (0.5)	14 (46.6)	46.6	99.4	93.3	91.7	91.8

Values are given as n (%) or %.

An optimal cutoff <450 Ω showed high sensitivity and specificity.

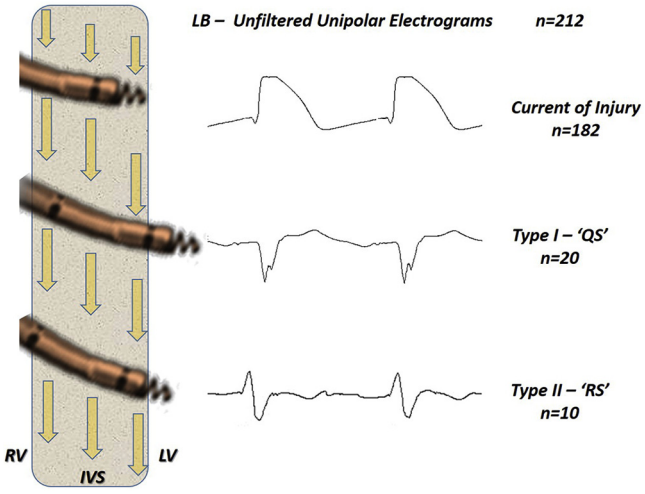

Figure 3 Types of unfiltered unipolar electrogram pattern during septal perforation. Type I (QS pattern) was noted in 67% and type II (RS pattern) in 33%. IVS = interventricular septum; LB = left bundle; LV = left ventricle; RV = right ventricle.

thickness, sheath support, yield of the septal myocardium, and presence or absence of scar. Jastrzebski et al[22] showed 4 unique lead behaviors during deployment in a cadaver simulation study: (1) helix-only penetration due to endocardial entanglement effect (43.1%); (2) helix-only penetration due to endocardial barrier effect (19.6%); (3) shallow or moderate penetration with drill effect (9.8%); and (4) progressive penetration resulting in deep septal deployment due to screw-driver effect (27.4%). They also demonstrated LV endocardium to be an effective barrier that protects against penetration despite additional rotations by the cadaver model. The reported incidence of SP during implantation varied between 0.3% and 3.2%.[11,23] The incidence in our study (14.1%) was higher than the previously reported data. The reasons for this higher incidence can be attributed to concerted efforts to achieve selective LBB capture by subendocardial deployment of the lead, narrower interventricular septal thickness (mean 10.1 mm in our study), and likely ethnicity of the study population. In all patients, the lead was safely repositioned at a new site without any complication.

Unipolar electrograms are generated by connecting the lead tip to the negative input of the recording amplifier (Workmate Claris, Abbott) (Figure 6). The positive input of the amplifier is connected to the Wilson central terminal.[24] The morphology of the unipolar electrograms from the lead tip indicates the direction of the wavefront. A positive deflection will be produced by a wavefront moving toward the recording electrode and a negative deflection as it moves away from the electrode. Depolarization of the tissue beneath the electrode coincides with maximum negative slope (–dV/dt) of the signal. During catheter ablation of tachyarrhythmias, unipolar electrograms are used to identify the site of origin, as "QS" complexes typically are recorded at the site of origin.[25,26] However, QS complexes also can be recorded if the exploring electrode is not in contact with the myocardium, as in our patients with perforation. In these patients,

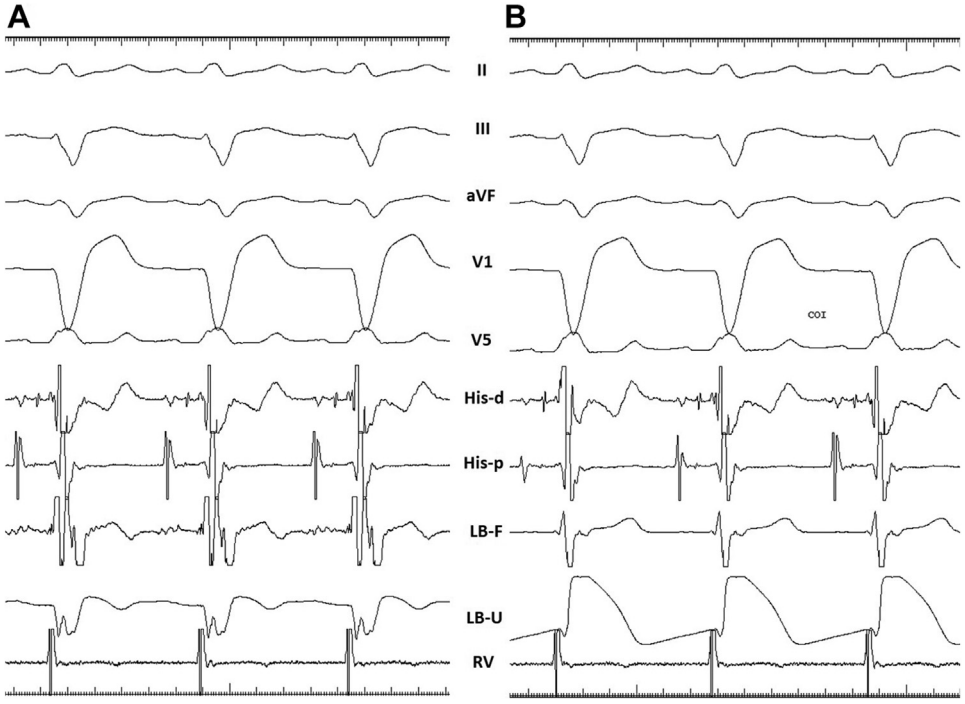

Figure 4 **A:** Type I perforation pattern with unfiltered unipolar electrogram (LB-U) showing QS pattern. **B:** Repositioning the lead at a new site showed good current of injury in the unfiltered electrogram. Filtered unipolar electrogram (LB-F) showed no significant change in injury pattern for diagnosing septal perforation. RV = right ventricle.

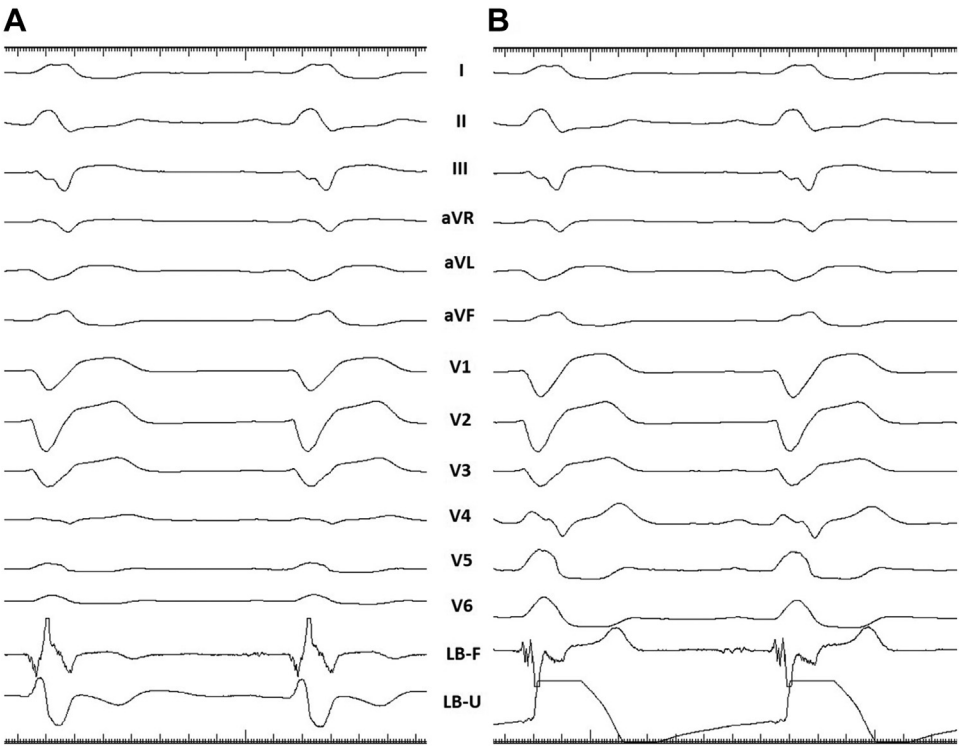

Figure 5 **A:** Type II perforation pattern with unfiltered unipolar electrogram (LB-U) showing RS pattern. **B:** Repositioning the lead at a new site showed good current of injury in the unfiltered electrogram. There was no significant injury pattern change in filtered unipolar electrogram (LB-F) for diagnosing septal perforation.

the initial negative deflection will be slurred due to far-field activation.[24] The potential disadvantage of the unipolar electrogram is the simultaneous recording of far-field signal. Nevertheless, a unipolar electrogram from the lead tip would provide better information than a bipolar electrogram about the SP, as the proximally positioned anode would mask the features of perforation.

Previous studies have suggested unipolar pacing impedance $<500\ \Omega$ to be a marker of SP.[15,16] In our study, we showed that a cutoff $<500\ \Omega$ had low specificity (86.6%), whereas $<400\ \Omega$ had low sensitivity (46.6%). An optimal value would be $<450\ \Omega$, which provided 100% sensitivity, 96.4% specificity, 82.3% positive predictive value, and 100% negative predictive value. Significant drop in the amplitude of COI in the unipolar electrogram (from 15.4 ± 11.6 mV to 0.9 ± 0.6 mV in our study) would indicate a possible SP. Hence, monitoring the amplitude of COI might help in identifying perforation during implantation. SP could be complete (helix into the LV cavity) or partial (proximal portion of the helix in contact with the septum). Accordingly, the unipolar electrogram would produce 2 different patterns: type I (QS) indicating complete perforation; and type II (RS) indicating partial helix contact with the septum. Although intracardiac echocardiography was not performed in our study, we hypothesize type II pattern to be a marker of partial contact by (1) demonstration of initial positive deflection due

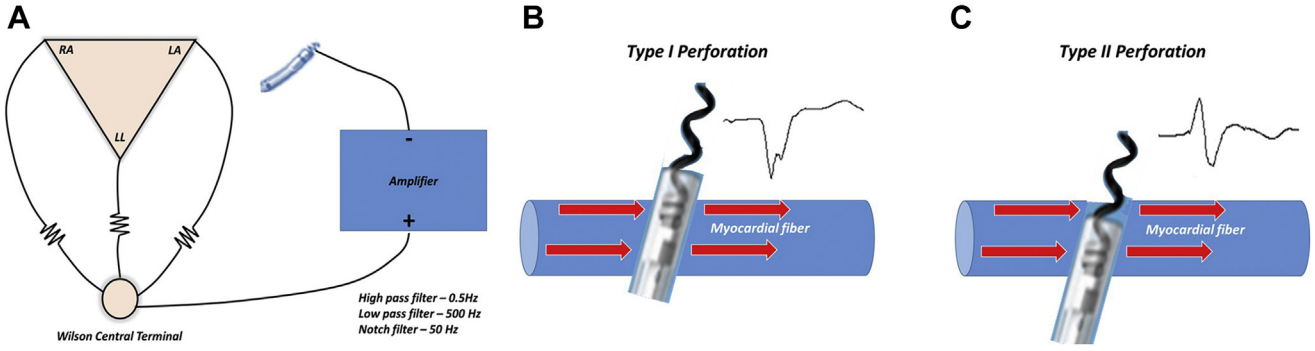

Figure 6 **A:** Setup for unfiltered unipolar electrogram in the electrophysiology system. Lead tip is connected to the negative input of the recording amplifier (Abbott). The positive input of the amplifier is connected to the Wilson central terminal. **B:** Type I pattern due to complete perforation would show QS (with or without notch) due to loss of contact with the myocardium. **C:** Type II pattern due to partial perforation would show an initial R wave due to wavefront traveling toward the proximal helix.

to wavefront traveling toward the proximal helix (RS pattern); (2) higher unipolar impedance and COI amplitude compared to type I, although not statistically significant; and (3) 80% of patients with type II showed capture during perforation compared to 35% with type II pattern.

LV subendocardium acts as a fibrous and elastic barrier while the lead moves from the right side to left side of the septum.[22] When the protection is breached by excessive rotations, perforation into the LV cavity occurs. Complete penetration of the helix into the cavity can be identified by loss of capture, absent COI, and drop in unipolar pacing impedance. Partial perforation (type II pattern in our study) has to be suspected in patients with "RS/rS" unipolar electrogram pattern with low-amplitude COI. Although associated with myocardial capture during pacing, the capture threshold would be high as demonstrated in 8 of 10 patients with type II pattern. All 30 patients underwent successful repositioning at a new site. Lead entry into the same site during reimplantation could be diagnosed by fluoroscopic landmark, absent template/fixation beats, similar paced QRS ,morphology and hypertransmission of rotations to the lead tip inside the septum. Presence of COI alone would not confer a new implantation site, as it can be seen reappearing while retracting the lead back into the septum from the LV cavity (Figure 2) after perforation.

The novel findings of our study would help in the diagnosis of SP using unipolar pacing parameters and avoid long-term complications. Although considered one of the concerns of LBBP, SP—when recognized promptly during implantation and treated by reimplantation—would be benign and not associated with unfavorable outcome.

Study limitations

This is the first study to analyze electrogram morphology and pacing impedance in patients with SP. This was a retrospective, single-center study using intracardiac electrograms and pacing parameters to identify SP. Intracardiac echocardiography was not used to demonstrate lead perforation during implantation and can be considered a major limitation of our study. Electroanatomic mapping during native rhythm was not performed to delineate the septal activation wavefront, so the "RS" pattern hypothesis requires further validation by electroanatomic mapping studies.

Conclusion

LBBP involves placement of the lead in the LV subendocardium, and the risk of complete or partial SP must be considered if pacing parameters are suboptimal. Prompt identification using unipolar electrograms and immediate repositioning at a different site will help in avoiding long-term thromboembolic complications.

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Double transition sign—a marker of left bundle branch capture during physiological pacing

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Ethics declarations

SSP: Consultant - Medtronic

Ethical approval

The study was conducted after getting the ethical committee approval.

The paper is not under consideration elsewhere. None of the paper's contents has been previously

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BRIEF COMMUNICATION

Axis deviation in nonischemic cardiomyopathy with left bundle branch block: Insights from left bundle branch pacing

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Abstract

Introduction

Biventricular pacing has shown excellent results in patients with heart failure and left bundle branch block (LBBB). Studies have shown that the patients with abnormal axis deviation may benefit less from cardiac resynchronization therapy (CRT) as compared to those with the normal axis. The exact reason for left axis deviation (LAD) in LBBB is not known but could be due to diseased left anterior fascicle, left ventricular enlargement, or due to advanced electrical remodeling.

Methods

The aim of the study was to analyze the incidence of LAD in nonischemic cardiomyopathy (NICM) with LBBB and the clinical outcomes following left bundle branch pacing (LBBP).

Results

We have included 64 consecutive patients with NICM and LBBB, who underwent successful LBBP. Patients were divided into two groups—Group I with baseline normal axis ($n = 40$; 63%) and Group II with LAD ($n = 24$; 37%). The mean axis changed from +23.6 ± 28.8° at baseline to +16.5 ± 35.1° and from −40.4 ± 10.3° at baseline to 7.08 ± 41.1° after LBBP in Group I and Group II, respectively. LBBP retained the normal axis in 93% of Group I patients and normalized the axis in 75% of Group II patients. The percentage changes in QRS duration, left ventricular ejection fraction, and left ventricular end-diastolic diameter were similar in both the groups (+40% vs. +32%; $p = .52$, +64% vs. +50%; $p = 0.34$, −8% vs. −6%; $p = .76$, respectively). Capturing the proximal LBB would correct the LAD by recruitment of left anterior fascicles and pacing proximal to the site of the septal breakthrough of the right bundle branch activation wavefront during LBBB.

Conclusion

LBBP as an alternative strategy for CRT could result in similar improvement in LBBB patients with LAD as in those with the normal axis.

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Left bundle branch–optimized cardiac resynchronization therapy (LOT-CRT): Results from an international LBBAP collaborative study group

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Background

Cardiac resynchronization therapy (CRT) based on the conventional biventricular pacing (BiV-CRT) technique sometimes results in broad QRS complex and suboptimal response.

Objective

We aimed to assess the feasibility and outcomes of CRT based on left bundle branch area pacing (LBBAP, in lieu of the right ventricular lead) combined with coronary venous left ventricular pacing in an international multicenter study.

Methods

LBBAP-optimized CRT (LOT-CRT) was attempted in nonconsecutive patients with CRT indications. Addition of the LBBA (or coronary venous) lead was at the discretion of the implanting physician, who was guided by suboptimal paced QRS complex, and/or on clinical grounds.

Results

RT was successful in 91 of 112 patients (81%). The baseline characteristi re
: mean age 70 ± 11 years, female 22 (20%), left ventricular ejection fracti 7%

9.8%, left ventricular end-diastolic diameter 62 ± 9 mm, N-terminal pro–B-type natriuretic peptide level 5821 ± 8193 pg/mL, left bundle branch block 47 (42%), nonspecific intraventricular conduction delay 25 (22%), right ventricular pacing 26 (23%), and right bundle branch block 14 (12%). The procedure characteristics were as follows: mean fluoroscopy time 27.3 ± 22 minutes, LBBAP capture threshold 0.8 ± 0.5 V @ 0.5 ms, and R-wave amplitude 10 mV. LOT-CRT resulted in significantly greater narrowing of QRS complex from 182 ± 25 ms at baseline to 144 ± 22 ms ($P < .0001$) than did BiV-CRT (170 ± 30 ms; $P < .0001$) and LBBAP (162 ± 23 ms; $P < .0001$). At follow-up of ≥3 months, the ejection fraction improved to 37% ± 12%, left ventricular end-diastolic diameter decreased to 59 ± 9 mm, N-terminal pro–B-type natriuretic peptide level decreased to 2514 ± 3537 pg/mL, pacing parameters were stable, and clinical improvement was noted in 76% of patients (New York Heart Association class 2.9 vs 1.9).

Conclusion

LOT-CRT is feasible and safe and provides greater electrical resynchronization as compared with BiV-CRT and could be an alternative, especially when only suboptimal electrical resynchronization is obtained with BiV-CRT. Randomized controlled trials comparing LOT-CRT and BiV-CRT are needed.

Graphical abstract

Figure thumbnail fx1

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Keywords

Biventricular pacing • Cardiac resynchronization therapy • Left bundle branch area pacing • QRS narrowing • Heart failure