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# Nepalese Heart Journal

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Nepalese Heart Journal (NHJ) is a biannual, peer-reviewed, open-access, international medical journal. NHJ publishes original research and critical reviews dealing with all disciplines of cardiovascular medicine. It is the official journal of the Cardiac Society of Nepal and is published twice a year (May and November). Each issue of NHJ publishes original articles, review articles, case reports, editorials and letters to the editor. Invited articles, editorials and review of selected topics will be published from time to time. Authors do not have to pay for the submission, processing or publication of articles in NHJ.

The Nepalese Heart Journal aims to facilitate a common portal for publication of wide ranging topics in cardiovascular research and clinical works. It aims to provide easy dissemination of research works to a variety of health workers and researchers.

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

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# Enhancing Transparency and Comprehensiveness of Scholarly Articles by the Use of Reporting Guidelines

**Apurb Sharma[1], Marisha Aryal[2]**

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Biomedical research is an ever evolving field. The integrity and impact of research work depends heavily upon transparent reporting. It is crucial for Nepalese Heart Journal to emphasize the significance of adhering to robust reporting guidelines. These guidelines are not just a checklist of items like requisites but now they are the foundation of scientific publications that assure clarity, reproducibility, and credibility.

Authors bear the responsibility of writing a narrative of their findings through adherence to reporting guidelines. Clear articulation of background and introduction, study design, methods, results, and interpretation and discussions empowers our readers to validate, and build upon our work. Simultaneously, our editors and reviewers play a pivotal role in endorsing these standards, ensuring that published content meets the benchmarks of excellence set forth by international reporting guidelines. However, the common fallacies in research reporting in healthcare are inability to properly conduct, write and publish the research article. Sometimes, entire studies are either not reported or are reported long after research is completed. Other times, studies are incompletely reported with crucial components being left out like who the study participants were, what interventions were used etc., or data and results are selectively reported and outcomes are omitted. Additionally contain inaccuracies like inconsistencies between abstracts and main text, statistical errors, harms are inadequately reported, data and graphs are confusing or misleading, and there is misinterpretation of results. The research becomes useless and falls victim to bad reporting.

## Elevating the Standards

By consistently incorporating reporting guidelines into our research endeavors, we elevate the standard of our research articles. This ensures our readers, reviewers, and researchers that our methodologies are designed as per standards, our analyses are accurate and our findings are presented with clarity. In doing so, we reinforce the credibility of our authors and the Nepalese Heart Journal as a beacon of excellence in biomedical research and publication.

Every scientific study is a narrative that describes what research question it aims to answer. To ensure its trust and contribution to the scientific literature, we must adopt and adhere to established reporting guidelines. The CONSORT guidelines for clinical trials, STROBE for observational studies, and CARE for case reports are the common guidelines and invaluable tools. These tools are tailored to amplify the transparency and completeness of research findings. Embracing these guidelines is not a constraint but an investment in the enduring impact of our contributions. Though these reporting guidelines were initially meant to be used by authors while preparing to write the final article, or even used as checklists before submission, we at Nepalese Heart Journal suggest that authors use these checklists while planning for the research and while writing the research proposal.

## The EQUATOR Network and Beyond

The EQUATOR (**E**nhancing the **QUA**lity and **T**ransparency **O**f health **R**esearch) Network is an international initiative that seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines. It is the first coordinated attempt to tackle the problems of inadequate reporting systematically and on a global scale; it advances the work done by individual groups over the last 15 years.

As we advocate for the adoption of reporting guidelines, we align ourselves with the global movement promoted by the EQUATOR Network. This consortium offers more than 600 resources and guidelines for various study designs and methodologies. Nepalese Heart Journal endorses the use of an appropriate reporting guideline when writing any health research manuscript. You can find the most commonly required reporting guidelines at https://www.equator-network.org/, which also provides general information on how to choose the correct guideline and why guidelines are important.

At minimum, your article should report the content addressed by each item of the identified checklist or state that the item was not considered in the study (for example, if you did not use blinding, your article should specify this). Meeting these basic reporting requirements will greatly improve the value of your manuscript, may facilitate/enhance the peer review process, and may enhance its chances for eventual publication.[1] We also highly recommend using tools like https://www.goodreports.org/ for easing the writing process and using the checklist.[2]

These guidelines have been incorporated in practice not only in the international journals but also in our national journals.[3]

In the domain of biomedical research, reporting guidelines are not constraints but catalysts for scientific advancement. They express our commitment to precision, transparency, and the relentless pursuit of knowledge. Let us, as contributors to the Nepalese Heart Journal, embrace these guidelines as instruments that fortify our scholarly legacy, enrich our academic discourse, and propel our research to global acclaim. Together, let's create a narrative of excellence that resonates far beyond the pages of our journal.

## References

1. Network, Equator. "What's Wrong with Health Reporting Today? | EQUATOR Network." www.equator-network.org/toolkits/using-guidelines-in-journals/whats-wrong-with-health-reporting-today/.

2. Struthers C, Harwood J, de Beyer JA, Dhiman P, Logullo P, Schlüssel M. GoodReports: developing a website to help health researchers find and use reporting guidelines. BMC Med Res Methodol. 2021 Oct 17;21(1):217. doi: 10.1186/s12874-021-01402-x. PMID: 34657590; PMCID: PMC8520646.

3. Sharma A, Aryal D. Guidelines for reporting health research: what authors should check before submitting an article. Journal of Society of Anesthesiologists of Nepal, 2016:3(2);53-54. https://doi.org/10.3126/jsan.v3i2.15606

Original Article

Nepalese Heart Journal 2024; Vol 21(1), 3-9

# Effect of Respiratory Proprioceptive Neuromuscular Facilitation in Phase One Cardiac Rehabilitation – A Randomized Controlled Trial

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## Abstract

**Background:** Patients undergoing coronary artery bypass graft (CABG) and valve replacement surgery often develop pulmonary complications in early post-operative period as results of decreased lung function and impaired cough reflex. The recent study aimed to determine and compare effectiveness of respiratory PNF to conventional physiotherapy in improving the pulmonary function and airway clearance in early period of CABG and valve replacement patients.

**Methods:** A Randomized control trial was conducted on 46 subjects with median sternotomy incision. Participants were assigned to either Group A (n=23) received phase one of cardiac rehabilitation or Group B (n=23) received phase one of cardiac rehabilitation and respiratory PNF. The sessions were carried for 30 min for five consecutive days twice a day. Outcome measure in the present study were peak flow meter, thoracic expansion, sputum volume, respiratory rate, heart rate and blood pressure. The outcome measures were evaluated on baseline and post 5 days of the intervention.

**Results:** within group analysis revealed that both the interventional and control groups improved significantly on all outcome measure with p-value less ($p<0.005$) than in all parameters expect for blood pressure, whereas a significant difference was seen in between group analysis in blood pressure (0.0500) and hear rate (0.0210).

**Conclusion:** the study concluded that phase one cardiac rehabilitation along with respiratory PNF are effective in improving the lung function, rate and depth of breathing, sputum clearance.

**Keywords:** phase one cardiac rehabilitation, respiratory PNF, CABG and valve replacement.

**DOI:** https://doi.org/10.3126/nhj.v21i1.65698

## Introduction

Due to a rise in the disease frequency, cardiovascular diseases have lately become more important in India. It is first among the top 5 causes of mortality of coronary vascular disease.[1]

CABG and valve surgery is carried through median sternotomy incision, which violates the chest wall. This has an impact on breathing pattern, due to which rate and depth of breathing is altered. Pain is experienced while breathing so individuals take shallow breaths that leads to less thoracic movement and causes decreased thoracic expansion of the chest.[2] After surgery patients commonly avoid coughing due to the prolonged effects of anesthesia and the absence of the cough reflex because of the pain at the incision site, which causes the cough to accumulate within the bronchial tree.

Cardiac rehabilitation increases exercise ability, quality of life, and mental health along with lowering mortality, morbidity, and unnecessary hospital admissions.[6] Following heart surgery, inpatient cardiac rehabilitation, also known as Phase I cardiac rehabilitation programs, is used to encourage early mobility and improve post-operative care.[5]

Breathing depth and rate can be changed by proprioceptive and tactile stimulation through neurophysiological facilitation. Stretching the intercostals is a productive treatment that enhances

respiratory muscle activation and breathing rhythm, increases diaphragmatic excursion, chest expansion, and elevation of the chest wall. Anterior basal lift is procedure that aids increasing respiratory muscle activity and in turn increases intrathoracic lung capacity, which helps to increase flow rate percentage.[7,8] According to Rood, the diaphragm is activated through co-contraction of the abdomen this technique stretches the abdominal muscles, which excites the muscular spindle and caused its homogeneous extrafusal muscles to contract. Post operative pulmonary complications are most common problems encountered by physiotherapist in early phase of cardiac rehabilitation. The purpose of the research was to evaluate and compare effectiveness of respiratory PNF in phase one cardiac rehabilitation.

## Method

Present study was conducted in Intensive Thoracic Unit of tertiary care hospital, in Belagavi city from January 2023 to July 2023. An ethical clearance from institution ethical committee was obtained and the study was registered under CTRI. A Randomized control trial was conducted on 46 subjects with median sternotomy incision. Participants were assigned to either Group A (n=23) received phase one of cardiac rehabilitation or Group B (n=23) received phase one of cardiac rehabilitation and respiratory PNF.An ethical clearance from institution ethical committee was obtained and the study was CTRI registered. Participants were screened for inclusion and exclusion criteria. Following the screening criteria eligible participants willing to participate in the study were provided with written inform consent. Simple random sampling was used to accomplish the randomization. The participants were randomly allotted in experimental and control group through envelop method. The study was a single blinded study. The statistician involved in the study was blinded to the intervention and control groups to ensure unbiased data analysis. Demographic data, pre and post assessment of the outcome measures were noted.

### Participants:

Inclusion criteria: Participants age group between 20- 70 years of both the genders. Participants who are willing to participate. Participants referred to physiotherapy. Participants who underwent median sternotomy incision.

Exclusion criteria: Participants who are uncooperative. Participants with hemodynamic instability. Critically ill patient. Participants with cognitive inability to understand the procedure.

### Intervention:

Similar post-operative medical treatment, nebulizer (budecort 0.5mg, duolin nebulizer solution), chest binder and incentive spirometer (800 cc/ sec) were administered to all the participants. Cardiac rehabilitation intervention with regards to the research, intervention study, started on POD2 for both the groups. The same therapist administered intervention in both the groups. Each participant was given a demonstration and detailed instructions about the intervention. Subjects were randomly allotted (envelop method) to Group A (control group) and Group B (experimental group). Intervention lasted for 20-30 minutes, twice a day for 5 days for both the groups.

**Control group:**

The treatment included standardized protocol of phase 1 cardiac rehabilitation.

Step 1: diaphragmatic breathing exercises. (5 repetitions, 3 sets), Active assisted ROM bilateral upper limb and lower limb (5repetitions, 3 sets) Ankle toe movements (5 repetitions, 3 sets), thoracic mobility exercises (5 repetitions, 3 sets)

Step 2: repeat step 1, sitting on the edge of the bed, active range of motion bilateral upper limb (shoulder abduction were limited to below 90 degree) and lower limb (5 repetitions, 4 sets)

Step 3: repeat step1, repeat step 2, supported room ambulation.

Step 4: repeat step1, repeat step 2, repeat step 3, trunk mobility exercises (5 repetitions, 3 sets), and unsupported ward ambulation (2 rounds)

Step 5: repeat step 4 and downstairs 2- flight (2 times/day), progression of ambulation[10]

**Intervention group:**

Similar intervention as above was followed along with phase 1 cardiac rehabilitation respiratory PNF was administered.

Inter costal stretch: subject positioning was standardized to supine flat, limbs in neutral position. The position of the therapist is behind the patient. First palpate the suprasternal notch. Then goes downward about 5cm. 2nd rib lies at the level of angle of Louis trace the finger laterally. The intercostal stretch technique was applied over 2nd- 6th rib bilaterally. The technique was given with the help of index finger. The direction of the pressure was downward towards the next rib. Technique was applied during expiration phase. It is applied for three breaths with 1-minute rest and three times repetition.[7]

Anterior Basal lifting: This procedure was performed by placing the hands under the posterior ribs of the supine patient and gently lifting the lower ribs upward. The lift is maintained and provides a maintained stretch and pressure posteriorly and stretch anteriorly as well. This technique was performed thrice and maintained for five breaths.[7,11]

Co contraction of abdomen: Provided by the therapist by pressing adequately pressure on the lower ribs and pelvis on the same side, so that the pressure is applied at the same angle. This technique will be performed thrice and maintained for five breaths.[11,12]

### Outcome measures:

**Peak expiratory flow meter:**

the patient was seated in a chair or in fowler's position on bed. The patient was instructed to inhale as deeply as they could and blow into the mouthpiece as rapidly as possible. The method was carried out three times for accurate measurements, and the average of the three was calculated.[8,3]

**Sphygmomanometer:**

diamond mercurial blood pressure monitor was used to access the blood pressure. The patient was seated comfortably supine position.[11]

**Respiratory rate:**

the patient was in supine position, with the use of stopwatch the patient's respiratory rate was counted for one minute.[11]

**Heart rate:**

pulse oximeter was used to access the heart rate. The patient was in supine position resting comfortably.

**Sputum volume:**

Sputum was collected in a container with markings to indicate the volume of sputum produced during each intervention (for each session/day)[13]. On POD 6, it was reported how much sputum had been expectorated overall (in mL) from POD 2 to POD 6.[6]

**Thoracic expansion measurements:**

The participants were sitting comfortably in upright position and the readings were taken at three level that is at the axillary, nipple, and xiphisternum were marked. They were instructed to take a few regular breaths first and then asked for full exhalation, followed by a full inhalation and a short holding period. Using a measuring tape, the difference between the maximal inhalation and exhalation was recorded while holding breath at each of the three levels.[7,8,27]

### Statistical analysis:

The various statistical measures such as mean, standard deviation, paired t test, Kolmogorov Smirnov test, Mann- Whitney U test was applied as required. Within group outcome measures like RR, HR blood pressure, thoracic expansion measurements, sputum volume and PEFR within group A and group B and between group A and group B was done using Kolmogorov Smirnov test, Mann-Whitney U test, dependent t test, independent t test.

## Results

A total of 60 participants were screened for inclusion criteria, of this 10 did not meet the inclusion criteria, 4 declined to participate. 46 participants met the inclusion criteria and were randomly divide into experimental and control group. All participants baseline and post intervention i.e., on 5th day score of respiratory rates, heart rate, peak flow rate, thoracic expansion measurements, sputum volume and blood pressure were noted.

Table 1 shows the age, gender, and BMI of the subject in both the groups. There was no statistical difference in age and BMI. Males accounted for more than half of these patients. (56.52% in control and 78.26% in intervention group)

Although respiratory rate improved markedly in both the groups through the intervention, The difference in effect size between the two intervention was minimal (table 2) (figure 1). Group B was found to be more effective than group A. Heart rate improved markedly in the group through the intervention, The difference in effect size between the two intervention was minimal (table 3). Group B was found to be more effective than group A. As the table 4 suggest that systolic blood pressure has shown significant improvement from baseline to day 5 for both within and between group analysis. The difference in effect size was seen more in group B as compared to group A (table 4). There was no significant statistical difference seen in diastolic blood pressure in both the groups. (Table 5) sputum volume markedly improved in the group through the intervention (table 6) (figure 2), The difference in effect size between the two intervention was minimal. Group B was found to be more effective than group A. Peak expiratory flow rate markedly improved in the group through the intervention (table 7) (figure 3). The difference in effect size between the two intervention was minimal. Group A was more effective than group B. Thoracic expansion measurement markedly improved in the group through the intervention (table 8). The difference in effect size between the two intervention was minimal. There was significant difference in group B at t4 level.

Table 1: demographic data

| Profile | group A | % | Group B. | % | p-value |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 13 | 56.52 | 18 | 78.26 | 0.1160 |
| Female | 10 | 43.48 | 5 | 21.74 | |
| **Age** | | | | | |
| <= 40 yrs. | 5 | 21.74 | 5 | 21.74 | |
| 41- 50 yrs. | 2 | 8.70 | 7 | 30.43 | 0.2890 |
| 51- 60 yrs. | 8 | 34.78 | 6 | 26.49 | |
| < 61 yrs. | 8 | 34.78 | 5 | 21.74 | |
| **Obesity** | | | | | |
| Normal | 3 | 13.04 | 5 | 21.74 | |
| Over-weight | 11 | 47.83 | 8 | 34.78 | 0.5990 |
| Obese | 9 | 39.13 | 10 | 43.48 | |
| Total | 23 | 100.00 | 23 | 100.00 | |

Table 2: Respiratory rate:

| | Within group | | | Between group | | |
|---|---|---|---|---|---|---|
| **Group** | **Changes from** | **Mean ± SD** | **p-value** | **Effect size** | **Mean ± SD** | **p-value** |
| Group A | BL-Day 5 | 7.48 ± 2.27 | 0.0001* | 0.8450 | 7.48 ± 2.50 | 0.3650 |
| Group B | BL-Day 5 | 11.91 ± 4.20 | 0.0001* | 0.8750 | 11.91 ± 2.90 | 0.6680 |

Table3: Heart rate:

| | Within group | | | Between group | | |
|---|---|---|---|---|---|---|
| **Groups** | **Changes from** | **Mean ± SD** | **p-value** | **Effect size** | **Mean ± SD** | **p-value** |
| Group A | BL-Day 5 | 8.96 ± 12.87 | 0.0002* | 0.8450 | 8.96 ± 14.83 | 0.0020* |
| Group B | BL-Day 5 | 11.48 ± 5.43 | 0.0001* | 0.8750 | 11.48 ± 5.62 | 0.4910 |

Table 4: Systolic blood pressure:

| | Within group | | | Between group | | |
|---|---|---|---|---|---|---|
| **Groups** | **Changes from** | **Mean ± SD** | **p-value** | **Effect size** | **Mean ± SD** | **p-value** |
| Group A | BL-Day 5 | 4.04 ± 8.21 | 0.0479* | 0.2000 | 4.04 ± 7.81 | 0.0130* |
| Group B | BL-Day 5 | 8.78 ± 10.94 | 0.0078* | 0.4340 | 8.78 ± 9.03 | 0.0500* |

Table 5: Diastolic blood pressure:

| | Within group | | | Between group | | |
|---|---|---|---|---|---|---|
| **Groups** | **Changes from** | **Mean ± SD** | **p-value** | **Effect size** | **Mean ± SD** | **p-value** |
| Group A | BL-Day 5 | -0.39 ± 7.20 | 0.9375 | 0.0020 | -0.39 ± 6.82 | 0.0870 |
| Group B | BL-Day 5 | 0.43 ± 10.58 | 0.9039 | 0.0900 | 0.43 ± 15.21 | 0.7390 |

Table 6: Sputum volume:

| | Within group | | | Between group | | |
|---|---|---|---|---|---|---|
| Groups | Changes from | Mean ± SD | p-value | Effect size | Mean ± SD | p-value |
| Group A | Pre-test to post-test | 12.35 ± 4.73 | 0.0001* | 0.8770 | 12.35 ± 4.63 | 0.4160 |
| Group B | Pre-test to post-test | 20.70 ± 4.29 | 0.0001* | 0.9610 | 20.70 ± 4.62 | 0.7490 |

Table 7: Peak expiratory flow rate:

| | Within group | | | Between group | | |
|---|---|---|---|---|---|---|
| Groups | Changes from | Mean ± SD | p-value | Effect size | Mean ± SD | p-value |
| Group A | Pre-test to post-test | 113.79 ± 25.92 | 0.0001* | 0.9530 | 113.79 ± 31.03 | 0.5450 |
| Group B | Pre-test to post-test | 161.45 ± 68.95 | 0.0001* | 0.8510 | 161.4 5± 84.04 | 0.1060 |

Table 8: Thoracic expansion measurement:

| Measure-ments | Groups | Within group | | | Between group | | |
|---|---|---|---|---|---|---|---|
| | | Chang-es from | Mean± SD | p-value | Effect size | Mean ± SD | p-value |
| At axilla | Group A | Pre-test to post-test | 0.48 ± 0.19 | 0.0001* | 0.8690 | 0.48 ± 0.19 | 0.8650 |
| | Group B | Pre-test to post-test | 0.59 ± 0.25 | 0.0001* | 0.8490 | 0.59 ± 0.25 | 0.8650 |
| At t4 level | Group A | Pre-test to post-test | 0.85 ±0.31 | 0.0001* | 0.8880 | 0.85 ±0.31 | 0.1100 |
| | Group B | Pre-test to post-test | 1.19 ± 0.33 | 0.0001* | 0.9320 | 1.19 ± 0.33 | 0.1450 |
| At xiphoid process | Group A | Pre-test to post-test | 0.83 ± 0.30 | 0.0001* | 0.8890 | 0.83 ± 0.30 | 0.6650 |
| | Group B | Pre-test to post-test | 0.83 ± 0.48 | 0.0001* | 0.7560 | 0.83 ± 0.48 | 0.7800 |

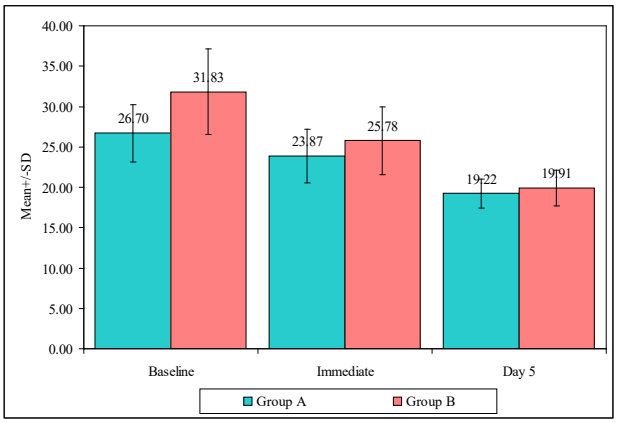


*Figure 1: Comparison of Group A and Group B with RR scores at different treatment time points*

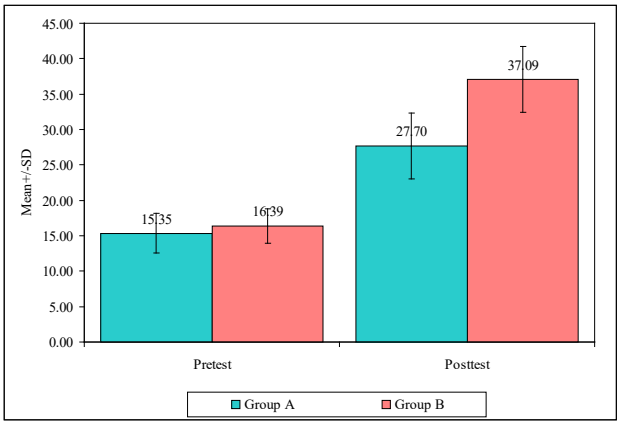


*Figure 2: Comparison of Group A and Group B with SPUTUM VOLUME scores at different treatment time points*

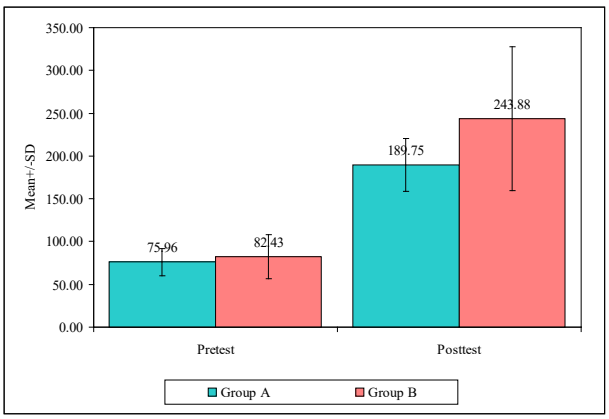


*Figure 3: Comparison of Group A and Group B with PEAK FLOW TARE scores at different treatment time points*

## Discussion

The present study had focused to evaluate the comparative effectiveness of respiratory PNF with conventional cardiac rehabilitation on RR, HR, blood pressure, PEFR, thoracic expansion flow rate and sputum volume in phase one cardiac rehabilitation. This study is a single blinded randomized controlled trial. The total

number of participant's recruited in the study were (n=46) in phase one cardiac rehabilitation with median sternotomy incision.

According to literature PNF procedures are applied to enhance pulmonary functioning and diaphragm muscle activity. Techniques are used to increase reaction and strengthen the muscles that control breathing. The direct application of these techniques, which are based on SHERRINGTON'S LAW OF SUCCESSIVE INDUCTION, stimulates the intrinsic muscles of respiration and increases the range of motion of the chest and diaphragm. This facilitates movement by inducing a stretch reflex and stimulating the intrinsic muscles of respiration.[13] A facilitator stimulus in the form of PNF respiration is generally established to induce responses to reflex respiratory movement approaches involve the use of external proprioceptive and tactile signals to produce reflex respiratory movement reactions that alters breathing frequency and depth. Abdominal co-contraction, intercostal stretch, and anterior stretch basal lift are some common PNF procedures.[17,18]

Chordiya SS et al research concluded that the values of pulmonary function and hemodynamic parameters were compared following traditional chest physiotherapy, and it was shown that PNF considerably improved the values of CPT pulmonary and hemodynamic parameters in mechanically ventilated patients[14]. The study statement by Kumar JA et al. our current research outcome by suggesting that phase one cardiac rehabilitation along with respiratory PNF shows enhancement in patient condition through decrease in RR, HR and Spo2.[15] During respiratory PNF, specific patterns of breathing and muscles contractions are employed to activate the muscle responsible for breathing, such as diaphragm, intercostal and accessory respiratory muscles. This activation leads to an increased awareness of breathing process, improving coordination and efficiency of breathing muscles. Therefore, in the recent study shows that post 5 days of intervention in post operated CABG and valve replacement patients there was significant difference in RR, heart rate. The study statement by Kumar JA et al. our current research outcome by suggesting that phase one cardiac rehabilitation along with respiratory PNF shows enhancement in patient condition through decrease in RR, HR and Spo2.[15]

The respiratory drive is controlled by input from sensory receptors in the airway, lungs, and respiratory muscles as well as central and peripheral chemoreceptors, the respiratory rate decreases when chest PNF is administered. The Golgi Tendon Organ (GTO), which is responsive to muscular stretch, regulates the contraction and relaxation of the respiratory muscles. This causes the muscle spindles to fire, which sends the signal to the central nervous system via the Alpha and Gamma motor neurons, which are directly in charge of starting the contraction of the muscle. IC Stretch causes the muscle fibers to contract and therefore resist the stretch because it enhances alpha motor neuron activity. The strength of the stretch reflex is controlled by gamma motor neurons, which innervate intrafusal muscle fibers of muscle spindles. Stretching the chest wall right before inhalation enhances gamma motor neuron discharge and improves alpha motor neuron activity.[7,8,16]

Thorat KD et al conducted a study on patients with spinal cord injury which was mainly based on pulmonary function and chest expansion[17]. it suggested that respiratory PNF enhanced pulmonary function and chest expansion in patients with spinal cord injury. In the present study significant difference was seen in thoracic expansion measurements at all three levels i.e., at axilla, at T4 level, at xiphoid process but effect size was more at t4 level in the experimental group. Respiratory PNF is a technique used to enhance respiratory muscle coordination and thoracic expansion. The mechanism of increase thoracic expansion after respiratory muscle PNF involves stimulating proprioceptive receptors in respiratory muscle which provides feedback to the central nervous system. The proprioceptive feedback from the activated respiratory muscles helps the CNS to fine-tune the timing and intensity of muscle contraction during breathing. This enhanced proprioceptive feedback for better synchronization of the respiratory muscles leading to a more effective and coordinated expansion of the chest during inspiration.

Mistry HM et al conducted a study and was based on RR, PEFR and chest expansion measurements in patient with chronic obstructive pulmonary disease[8]. The study concluded that respiratory PNF was effective in improving RR, PEFR, and chest expansion. In the present study it shows that post 5 days of intervention in CABG and valve replacement surgery it was effective in reducing RR, increasing PEFR and thoracic expansion measurements. Increase in PEFR after introducing respiratory PNF is due to the following: improving respiratory muscle strength, enhanced coordination i.e., effective breathing requires precise coordination between respiratory muscles, increased thoracic mobility, reduced airway resistance i.e., improved respiratory muscle strength and coordination along with increased thoracic mobility, can reduce this resistance. When the respiratory muscle work optimally, they can effectively overcome any resistance encountered in the airways, leading to smooth and increased peak expiratory flow rate.

Amin R et al conducted a study on patients undergoing CABG which was mainly based on pulmonary ventilation regimen to improve ventilation and avoid post operative complications in CABG patients,[10] similar observations were seen in the present study using incentive spirometry along with respiratory PNF and CRP enhances sputum clearance and improve pulmonary ventilation.

The primary muscle of breathing is diaphragm. Through its insertion at the lower ribs, the diaphragm exerts direct pressure on the rib cage, which the abdominal muscles then use to lower intrathoracic pressure. Effective coughing is influenced by the strength of the abdominal muscles. Individuals with weak abdominal muscles exhibit inefficient coughing, which can accumulate secretions and cause infections, which can impair pulmonary function.[16] This results in functional interruption of the diaphragm movement by reflex suppression of the phrenic nerve.[10,15,19,20]

In the present study CRP have significant effect on hemodynamic responses such as heart rate and blood pressure. Stable HR, SBP, and DBP readings during both PNF stimulations show that the procedures were properly tailored to the patients' needs. Aggressive stimulation may cause tachycardia, as well as discomfort and fatigue. The comparison between the control and interventional group showed significant improvement in heart rate and SBP and DBP post intervention in both the groups. O' Farrell et al found that low intensity exercise training significant improvement in SBP and DBP. The result of this study can be supported by Ghashghaei FE et al, which characterized that cardiac rehabilitation significantly improves functional capacity and some hemodynamic responses post CABG.[23,4] Therefore, the results of this study provide preliminary evidence where respiratory PNF along with cardiac rehabilitation was an effective treatment to improve chest expansion, peak expiratory flow rate, sputum volume and blood pressure and

to lower the heart rate, respiratory rate in post operated CABG and valve replacement patients.

The current study had several limitations. Initially recruiting larger sample size was difficult due to post operative complications such as prolonged mechanical ventilation and oozing from suture site. Furthermore, patients with low-risk postoperative pulmonary complications were included in the study. Finally, the long-term effect of respiratory proprioceptive neuromuscular facilitation in phase one cardiac rehabilitation were not monitored. Further studies in patients with different risk and longer duration are suggested to be carried out.

The present study concludes that cardiac rehabilitation along with respiratory PNF was associated with enhanced respiratory muscle strength and function, effective in improving rate and depth of breathing, sputum volume and pulmonary function in post operated CABG and valve surgeries.

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**Conflict of interest:** There is no conflict of interest.

## REFERENCES:

1. Gupta R, Guptha S, Sharma KK, Gupta A, Deedwania P. Regional variations in cardiovascular risk factors in India: India Heart Watch. World Journal of Cardiology. 2012. 4(4): 112-120 . doi: 10.4330/wjc.v4.i4.112. PMCID: PMC3342579
2. Bujar-Misztal M, Chciałowski A. Influence of proprioceptive neuromuscular facilitation on lung function in patients after coronary artery bypass graft surgery. InClinical Medicine Research 2018 (pp. 11-17). Springer, Cham. doi: 10.1007/5584_2018_243. PMID: 30128938
3. Ragnarsdottir M, Kristjánsdóttir Á, Ingvarsdóttir I, Hannesson P, Torfason B, Cahalin LP. Short-term changes in pulmonary function and respiratory movements after cardiac surgery via median sternotomy. Scandinavian cardiovascular journal. 2004 Jan 1;38(1):46-52. Doi: 10.1080/14017430310016658
4. Ghashghaei FE, Sadeghi M, Marandi SM, Ghashghaei SE. Exercise-based cardiac rehabilitation improves hemodynamic responses after coronary artery bypass graft surgery. ARYA atherosclerosis. 2012;7(4):151. PMCID: PMC3413083
5. Bhutiani E. A Protocol Guided Inpatient Cardiac Rehabilitation Program in Patients Following Coronary Artery Bypass Graft Surgery to Reduce Post-Operative Complications and Improve Functional Capacity (Doctoral dissertation, Weill Medical College of Cornell University).
6. Dalal HM, Doherty P, Taylor RS. Cardiac rehabilitation. Bmj. 2015 Sep 29;351 .doi: 10.1136/bmj.h5000
7. Gupta P, Nambi GS, Gupta G et.al. Effect of intercostal stretch technique and anterior basal lifting technique on respiratory rate, saturation of peripheral oxygen and heart rate amoung ICU patients. Int J Health Sci Res.2014;4(2):26-30.
8. Mistry HM, Kamble RV. Immediate effect of Chest Proprioceptive Neuromuscular Facilitation on Respiratory Rate, Chest Expansion and Peak Expiratory Flow Rate in patients with Chronic Obstructive Pulmonary Disease. Int J Physiother Res. 2021;9(1):3723-29. DOI: https://dx.doi.org/10.16965/ijpr.2020.175
9. Jage B, Thakur A. Effectiveness of Acapella along with institutional based chest physiotherapy techniques on pulmonary functions and airway clearance in post-operative CABG patients. Hong Kong Physiotherapy Journal. 2022 Dec 15;42(02):81-9. doi: 10.1142/S101370252250007X
10. Amin R, Alaparthi GK, Samuel SR, Bairapareddy KC, Raghavan H, Vaishali K. Effects of three pulmonary ventilation regimes in patients undergoing coronary artery bypass graft surgery: a randomized clinical trial. Scientific Reports. 2021 Mar 24;11(1):67. doi: 10.1038/s41598-021-86281-4
11. KUMARESAN P, RAVICHANDRAN U, SINGH D, SERAMAN M. Effect of Short-term Respiratory Proprioceptive Neuromuscular Facilitation on Peak Expiratory Flow Rate and Six-minute Walk Test in Patients with Stable Chronic Obstructive Pulmonary Disease: A Quasi-experimental Study. Journal of Clinical & Diagnostic Research. 2022 Jun 1;16(6). doi: 10.7860/JCDR/2022/55928.16458
12. Pryor JA and Webber BA (2002): Physiotherapy techniques. In Pryor JA and Prasad SA (Eds): Physiotherapy for Respiratory and Cardiac Disorders. (3rd ed.) London: Churchill Livingstone pp. 161-242.
13. Vidhyadhari BS, Madavi K. Influence of proprioceptive neuromuscular facilitation techniques on diaphragm muscle activity and pulmonary function in subjects with Guillain-Barre syndrome. Indian J Physiother Occup Ther. 2015 Apr;9:24-8. doi: 10.5958/0973-5674.2015.00047.7
14. Chordiya SS, Kazi A, Shetty A, Gunjal S, Lamuvel M, Bhoir T. Effect of respiratory proprioceptive neuromuscular facilitation technique with chest physiotherapy in mechanically ventilated Organophosphorus poisoning patients. International Journal of Multidisciplinary Research and Development. 2017;4(6):01-6.
15. Kumar, A. S. et al. Comparison of fow and volume incentive spirometry on pulmonary function and exercise tolerance in open abdominal surgery: A randomized clinical trial. J. Clin. Diagn. Res. 10, KC01–KC06 (2016). doi: 10.7860/JCDR/2016/16164.7064
16. Magee DJ, Manske RC. Orthopedic physical assessment-E-Book. St. Louis, MO: Elsevier Health Sciences. 2014.
17. Thorat KD. Effectiveness of Respiratory Proprioceptive Neuromuscular Facilitation Techniques on Pulmonary Functions in Patients with Spinal Cord Injury-A Pilot Study. doi: 10.52403/ijshr.20211026
18. Ashtankar AP, Kazi A, Chordiya S. Comparative effect of Proprioceptive Neuromuscular Facilitation (PNF) and chest physiotherapy with chest physiotherapy alone on SP02, heart rate, respiratory rate, & lung compliance in mechanically ventilated patient. J Pharm Sci Res. 2019;11(10):3514-8.
19. Dias, C. M. et al. Tree physiotherapy protocols: Efects on pulmonary volumes afer cardiac surgery. J. Bras. Pneumol. 37, 54–60 (2011). doi: 10.1590/S1806-37132011000100009
20. Oikkonen, M., Karjalainen, K., Kähärä, V., Kuosa, R. & Schavikin, L. Comparison of incentive spirometry and

intermittent positive pressure breathing afer coronary artery bypass graf. Chest 99, 60–65 (1991). doi: 10.1378/chest.99.1.60

21. Gamsu G, Singer MM, Vincent HH, Berry S, Nadel JA. Postoperative impairment of mucous transport in the lung. American Review of Respiratory Disease. 1976 Oct;114(4):673-9.

22. Furukawa H, Kangai K, Minami K, et al. Initial clinical experience of early cardiac rehabilitation for very elderly patients over 85 years old following open heart surgery. Kyobu Geka 2012; 65: 440–445. PMID: 22647324

23. O'Farrell P, Murray J, Huston P, LeGrand C, Adamo K. Sex differences in cardiac rehabilitation. The Canadian Journal of Cardiology. 2000 Mar 1;16(3):319-25. PMID: 10744794

24. Johansson EL, Ternestén-Hasseus E, Olsén MF, Millqvist E. Physical therapy treatment of impaired chest mobility in patients with airway sensory hyperreactivity. Physiotherapy Research International. 2017 Apr;22(2): e1658. doi: 10.1002/pri.1658

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Original Article

Nepalese Heart Journal 2024; Vol 21(1), 11-19

# Effects of Flaxseed on Blood Pressure in Patients Taking Antihypertensive Drugs: A Randomized Trial

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## Abstract

**Background:** The cardiovascular protective effects of consuming flaxseed, such as improving lipid profile and reducing inflammatory markers, have been studied in both animals and humans. This study aimed to assess the effects of flaxseed in patients taking antihypertensives and compare their blood pressure before and after daily consumption of flaxseed on days 0, 45, and 90.

**Methods:** This randomized trial was registered at ClinicalTrials.gov (Identifier: NCT0475950). A single-blind, parallel-group, prospective interventional randomized clinical trial was conducted using a lottery sampling method. Systemic blood pressure measurements were taken on days 0, 45, and 90. Descriptive statistics, including percentages, means, and standard deviations (SD), were calculated and presented. Inferential analyses involved independent t-tests and paired t-tests.

**Results:** Out of 72 hypertensive patients, 34% were males and 38% were females. There were no withdrawals from the study post-enrollment. The mean age of enrolled patients was 55.38 years, and the mean BMI was 26.53 kg/m$^2$. After 90 days, the flaxseed group demonstrated a significant reduction in mean Systolic Blood Pressure (SBP) from 151.62 to 131.89 mmHg, equating to a 13.01% decrease versus 4.77 % reduction in placebo group (p-value = 0.001). While there was also a reduction in mean Diastolic Blood Pressure (DBP) from 94.86 to 81.08 mmHg, corresponding to a 14.53% decrease in flaxseed group versus 5.7% reduction in placebo group, this change was not statistically significant (p-value = 0.082).

**Conclusion:** Flaxseed, when given alongside antihypertensives to patients with hypertension, can be effective and safe in maintaining blood pressure, thus reducing the risk of cardiovascular diseases.

**Keywords:** antihypertensives; flaxseed; clinical trial; cardiovascular diseases; blood pressure

**DOI:** https://doi.org/ 10.3126/nhj.v21i1.65663

## Background

Hypertension, a significant predisposing factor for fatality worldwide, is responsible for approximately 8.5 million cardiovascular deaths globally. Extensive research is underway to find cost-effective medications for managing hypertension.[1] The economic impact of treating hypertension is substantial, with an estimated direct and indirect cost of $51.2 billion in 2012-2013 and a projected total direct cost of $200 billion by 2030.[1]

Accurate diagnosis and evidence-based treatment of hypertension can effectively reduce cardiovascular events, disability, and death among patients.[2] The American Heart Association has updated its recommendations, defining hypertension as a blood pressure reading of 130/80 mm Hg or higher and providing new treatment guidelines that include lifestyle modifications and blood pressure-lowering drugs.[3] Hypertension is often referred to as the "silent killer" due to the absence of symptoms or warning signs, highlighting the importance of regular blood pressure monitoring.4 However, challenges persist in diagnosis and treatment due to reliance on cuff evaluations and the potential for long-standing, unpredictable, and side effect-linked treatment regimens.[4] Furthermore, only a fraction of patients who require blood pressure-lowering drugs have access to effective and affordable medications.[4]

Controlling elevated blood pressure, along with addressing other risk factors such as diabetes, dyslipidemia, and smoking, is crucial for preventing atherosclerotic diseases. Nutritional factors, accounting for approximately 40% of all cardiovascular diseases, including hypertension, have been studied in relation to the beneficial effects of flaxseed supplementation as a source of alpha-linolenic acid (ALA).[5-8]

The increasing prevalence of non-communicable diseases (NCDs) in Nepal, where NCDs account for nearly 50% of total deaths and cardiovascular disease represents 25% of these deaths, highlights the importance of addressing hypertension as a crucial risk factor.[9] Nepal has one of the highest proportions of hypertensive individuals, with an estimated prevalence of 27.3%.[9] Studies conducted in eastern Nepal have reported a hypertension prevalence of 33.9% among adults aged 20 years and above, emphasizing the need for interventions targeting cardiovascular risk factors.[10]

Flaxseed, derived from Linum usitatissimum L., is rich in alpha-linolenic acid, an omega-3 fatty acid. Its cardiovascular protective effects demonstrated through improvements in lipid profiles and reductions in inflammatory markers, have been investigated in both animal and human studies.[11-18] This study aims to further explore the potential use of flaxseed as a promising anti-hypertensive medication in our specific settings as no such flaxseed intervention in hypertensive patients were conducted yet in Nepal till date.

## Methods

### 2.1. Study design

The present study was a single-blind, two parallel-group, prospective interventional randomized clinical trial conducted on hypertensive patients visiting the Medicine OPD [Out Patient Department) of B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

#### 2.1.1. Protocol registration

After receiving approval from the Institutional Review Committee, BPKIHS, and the Nepal Health Research Council, Kathmandu, the study was registered on clinicaltrials.gov with the registration number ID: NCT04759508.

#### 2.1.2. Ethical statement

The study was approved by the Institutional Review Committee at BPKIHS, Dharan (Reference no: 347/077/078-IRC), and the Nepal Health Research Council, Kathmandu-Nepal (Reference no: 2608). Eligible participants received detailed information about the study, including potential adverse drug reactions, before providing informed consent and information on demographic factors and medical history.

### 2.2. Participant selection

#### 2.2.1. Inclusion criteria

The inclusion criteria for participants were as follows:

- Patients aged 18 years and above with a confirmed diagnosis of hypertension
- Patients who agreed to take only physician-advised medicine.
- Patients who strictly followed the advised diet.
- Patients taking a single antihypertensive drug with equivalent doses.

#### 2.2.2. Exclusion criteria

The following individuals were excluded:

- Patients suffering from serious or recurrent infections.
- Pregnant or breastfeeding women, immunodeficiency or HIV patients.
- Patients presenting with any mental abnormality that could impede or be influenced by the study procedure.
- Patients with a history of bleeding disorders.
- Hypersensitivity reaction or allergy to flaxseed.
- History of surgery within the past 6 weeks.
- Patients who did not give informed consent.
- Alcohol consumption > 30 U/day.
- Cigarette smoking > 2 packs/day.
- Patients taking multiple antihypertensive drugs.

### 2.3. Randomization and blinding

Randomization was conducted using the "lottery method," which is a common and basic randomization technique. Interventional and placebo groups were numbered on separate slips of paper of the same size, shape, and color. The slips were folded, mixed in a container, and a blindfolded selection was made. The required number of slips was selected for the desired sample size, and the respective groups were allocated in a sequence.

### 2.4. Sample size calculation

The number of participants required in each group was calculated using a power and sample size program. The sample size estimation for this study was based on the following formula:

Using the formula of two samples mean comparison: -

$n = \{2\sigma^2 (Z\alpha/2+Z\beta)^2\}/ (\bar{x}1 - \bar{x}2)^2$ where, σ= combined standard deviation,

Here, σ1=11, σ2=10

Zα/2 = 1.96 for a 95% confidence level

This set of data was decided by taking reference from the result obtained by Levya et al. (11)

### 2.5. Intervention

After obtaining clearance from the IRC and NHRC, randomization was conducted, assigning participants to either the Interventional group receiving Flaxseed Capsule 500 mg or the placebo group receiving a look-alike capsule with no therapeutic effect. Both groups were instructed to take their respective capsules twice a day along with the anti-hypertensive drug Amlodipine 5 mg. On the first day of enrollment, before the start of the intervention, the blood pressure of all enrolled subjects was measured. Demographic data and recorded blood pressure were documented on Day 0. Subjects were then given their respective capsules, and the first follow-up was conducted on the 45th day. Finally, subjects were followed up again on the 90th day. The proforma, which included patients' socio-demographic data, blood pressure values, adverse drug reactions (ADR), and drug interactions, was completed. The data were appropriately coded, entered into MS Excel, and subsequently analyzed using SPSS v20 for further analysis.

#### 2.5.1 Subject withdrawal

The study team made every reasonable effort to complete the study. If any subject wished to withdraw from the study at any time, he or she was permitted to do so. Every reasonable effort was made to complete a final assessment.

A subject may withdraw from the study in any of the following circumstances:

1. Serious adverse events
2. Major violation of the protocol
3. Withdrawal of consent
4. Occurrence of any systemic illness during the study period requiring the intake of other drugs
5. Dose modification of equivalent antihypertensive medications required as per the physician's discretion.

### 2.6 Outcome measures

#### 2.6.1 Primary outcome measures

- To assess the effects of Flaxseed in patients taking antihypertensive drugs.

#### 2.6.2 Secondary outcome measures

- To compare the blood pressure of patients before and after daily consumption of Flaxseed on Day 0, 45$^{th}$ day, and 90$^{th}$ day.
- To analyze adverse effects after daily consumption of Flaxseed.

### 2.7 Statistical analysis

The intention-to-treat (ITT) population was used for the efficacy analysis. For safety analysis, all randomized participants who took at least one dose of any investigational drug were included. Data collected from the study were coded and evaluated using MS Excel 2013. SPSS 20v was used for per-protocol statistical analysis. Descriptive statistics, including percentages, means, and standard deviations, were calculated and presented graphically and in tables. For inferential analysis, independent t-tests and paired t-tests were applied to determine significant differences between the groups taking both amlodipine and flaxseed and the other groups taking Amlodipine and placebo drugs. Other relevant variables were calculated at a 95% confidence interval, with $p<0.05$.

Procedure-

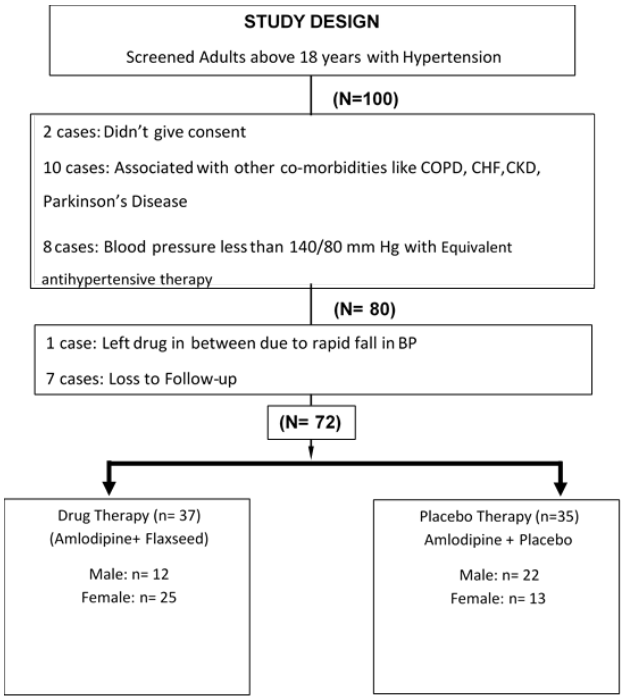


Figure 1: CONSORT Diagram of Study

## Results

The study was conducted from September 2020 to September 2021, and it included hypertensive patients above the age of 18 who visited the medicine OPD. A total of 72 hypertensive patients participated in the study, comprising 34 males and 38 females. They were divided into two groups: Drug Therapy group (37 patients) and the Placebo group (35 patients). There were no dropouts after the final enrollment. The mean age of the enrolled patients was 55.38 years, and the mean BMI was 26.53 kg/m2. Six patients experienced side effects such as nausea, constipation, and hypotension due to Flax capsule intake, and they were appropriately managed at the Medicine OPD. Vitals were stable at the time of the OPD visit for all those six patients. Proton pump inhibitor (Omeprazole tablet), Laxative (Lactulose syrup), Oral rehydration therapy, reassurance, and proper counseling to encourage further participation in this study was assured. The detailed results of this Randomized Single Blind Placebo Controlled Trial are presented below.

Table 1: Baseline characteristics of the study population

| | Drug Therapy n=37 (51.4%) | Placebo Therapy n=35 (48.6%) |
|---|---|---|
| **Gender** | | |
| Male | 11 (29.7) | 22 (62.9) |
| Female | 26 (70.3) | 13 (37.1) |
| Age in years | | |
| 18-40 | 3 (8.1) | 3 (8.6) |
| 41-60 | 21 (56.8) | 24 (68.6) |
| >60 | 13 (35.1) | 8 (22.9) |
| **District** | | |
| Sunsari | 32 (86.5) | 26 (74.3) |
| Morang | 0 (0) | 5 (14.3) |
| Siraha | 1 (2.7) | 2 (5.7) |
| Saptari | 3 (8.1) | 1 (2.9) |
| Dhankuta | 1 (2.7) | 1 (2.9) |
| **Religion** | | |
| Hindu | 32 (86.5) | 31 (88.6) |
| Muslim | 1 (2.7) | 1 (2.9) |
| Christian | 3 (8.1) | 2 (5.7) |
| Kiratis | 0 (0) | 1 (2.9) |
| Buddhist | 1 (2.7) | 0 (0) |
| **Marital status** | | |
| Married | 37 (100) | 35 (100) |
| Unmarried | 0 (0 %) | 0 (0 %) |
| **Residence** | | |
| Semi-Urban | 34 (91.9%) | 34 (97.1) |
| Rural | 3 (8.1%) | 1 (2.9) |
| Education | | |
| Literate | 17 (45.9%) | 25 (71.4) |
| Illiterate | 20 (54.1%) | 10 (28.6) |
| Occupation | | |
| Business | 5 (13.5%) | 7 (20) |
| Homemaker | 20 (54.1%) | 10 (28.6) |
| Teacher | 1 (2.7%) | 3 (8.6) |
| Farmer | 5 (13.5%) | 8 (22.9) |
| Service | 5 (13.5%) | 7 (20) |
| Sweeper | 1 (2.7%) | 0 |
| **Duration of Hypertension (in years)** | | |
| 1 to 5 | 21 (56.8%) | 29 (82.8) |
| 6 to 10 | 6 (16.2%) | 3 (8.6) |
| 11 to 15 | 8 (21.6%) | 3(8.6) |
| 16 to 20 | 1 (2.7%) | 0 (0) |
| >20 | 1 (2.7%) | 0 (0) |
| Family History | | |
| Yes | 17 (45.9%) | 20 (57.1) |
| No | 20 (54.1%) | 15 (42.9) |
| **Smoking** | | |
| Yes | 13 (35.1%) | 20 (57.1) |
| No | 24 (64.9%) | 15 (42.9) |
| **Alcohol intake** | | |
| Yes | 11 (29.7%) | 25 (71.4) |
| No | 26 (70.3%) | 10 (28.6) |
| **BMI** | | |
| <18.5 | 1 (2.7%) | 0 (0) |
| 18.5-22.9 | 2 (5.4%) | 8 (22.9) |
| 23-24.9 | 9 (24.3%) | 9 (25.7) |
| 25-29.9 | 17 (45.9%) | 14 (40) |
| >30 | 8 (21.6%) | 4 (11.4) |

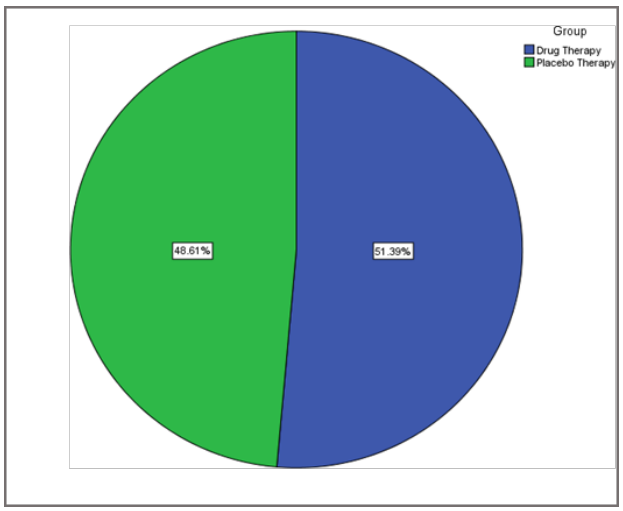


*Figure 2: Distribution of Groups in Patients Receiving Intervention*

Figure 2 displays the distribution of patients in the intervention study. Out of the total 72 patients, 51.39% received drug therapy consisting of flax capsules with Amlodipine, while 48.61% received placebo therapy consisting of placebo capsules with Amlodipine, as illustrated in Figure 2.

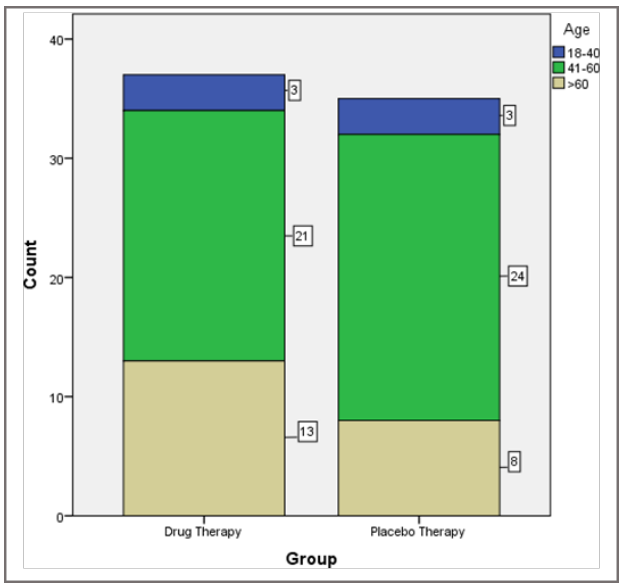


*Figure 3: Age distribution among patients receiving intervention*

Figure 3 presents the age distribution of the 72 enrolled patients. Among them, 63% fell within the 41-60 years age group, 29% belonged to the above 60 years age group, and only 8% were in the 18-40 years age group. These patients had hypertension and were undergoing antihypertensive drug therapy for a specified duration, as depicted in Figure 3.

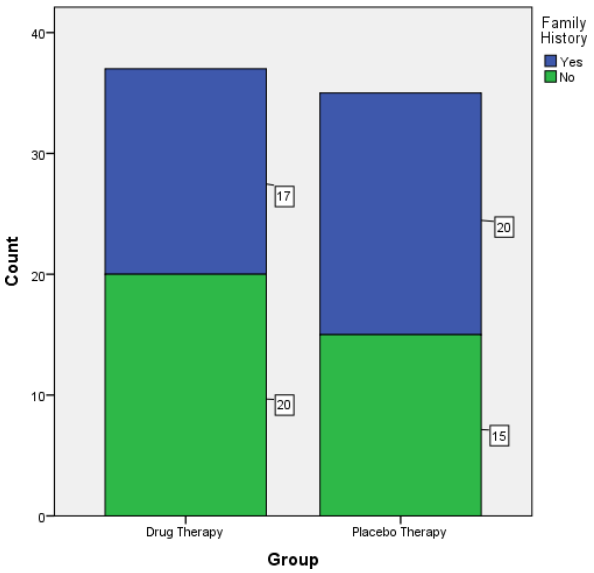


*Figure 4: Prevalence of family history among enrolled patients*

In Figure 4, the comparison between enrolled patients receiving drug therapy (Flax capsule and Amlodipine together) and placebo therapy (Placebo capsule and Amlodipine together) reveals no significant difference in the prevalence of family history of hypertension. Specifically, 51% of the patients reported a positive family history, while 49% reported a negative family history of hypertension, as depicted in Figure 4.

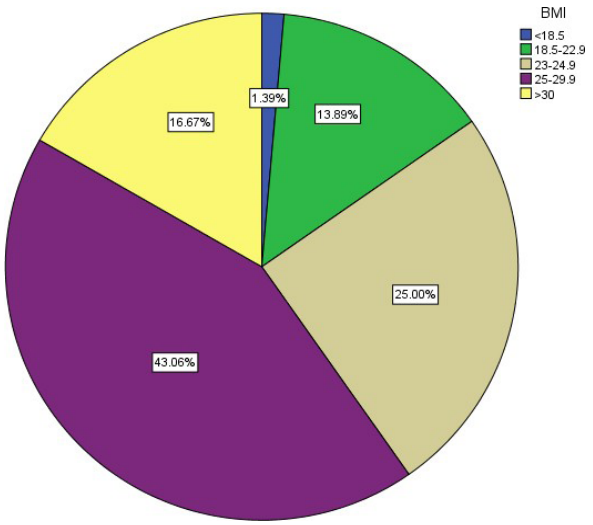


*Figure 5: Distribution of BMI among patients receiving the intervention*

Given the significant correlation between BMI and SBP/DBP, Figure 5 illustrates the distribution of BMI among the enrolled patients. Approximately 60% of the patients fall within the obese category, followed by 25% in the overweight category, and around 14-15% within the normal category, as depicted in Figure 5.

Systolic Blood Pressure and Diastolic Blood Pressure at Day 0

**Table 2:** SBP and DBP at Day 0 and Independent – Samples T-test

| Group | Drug Therapy | Placebo Therapy | p-value* |
|---|---|---|---|
| SBP Day 0 | 151.62±13.020 mm of hg | 150.86± 10.396 mm of hg | 0.671 |
| DBP Day 0 | 94.86±8.035 mm of hg | 90 ± 7.060 mm of hg | 0.411 |

Table 2 summarizes that the SBP and DBP datasets in both groups before the intervention at Day 0 are statistically non-significant.

**Table 3:** Comparison of SBP and DBP following drug therapy and Amlodipine using Paired-Samples t-test

| Data Comparison | Paired Differences | p-Value |
|---|---|---|
| SBP Day 0 - SBP Day 45 | 14.324 ± 12.811 | 0.001 |
| SBP Day 45 - SBP Day 90 | 5.405 ± 7.301 | 0.001 |
| SBP Day 0 - SBP Day 90 | 19.730 ± 12.799 | 0.000 |
| DBP Day 0 - DBP Day 45 | 11.892 ± 7.393 | 0.003 |
| DBP Day 45 - DBP Day 90 | 1.892 ± 5.695 | 0.051 |
| DBP Day 0 - DBP Day 90 | 13.784 ± 8.284 | 0.002 |

Table 3 summarizes that there is a significant reduction in systolic and diastolic blood pressures following drug therapy and Amlodipine when comparing Day 0 to Day 45, Day 45 to Day 90, and Day 0 to Day 90, except for the comparison of DBP Day 45 - DBP Day 90, which appears to be statistically non-significant.

**Table 4:** Comparison of SBP and DBP following placebo therapy and Amlodipine using Paired-Sample t-test

| Data Comparison | Paired Differences | p-Value |
|---|---|---|
| SBP Day 0 - SBP Day 45 | 5.429 ± 7.413 | 0.001 |
| SBP Day 45 - SBP Day 90 | 1.714 ± 5.137 | 0.063 |
| SBP Day 0 - SBP Day 90 | 7.143 ± 7.101 | 0.000 |
| DBP Day 0 - DBP Day 45 | 4.000 ± 6.945 | 0.001 |
| DBP Day 45 - DBP Day 90 | 1.143 ± 5.298 | 0.211 |
| DBP Day 0 - DBP Day 90 | 5.143 ± 6.585 | 0.003 |

Table 4 summarizes the changes in systolic and diastolic blood pressures following placebo therapy and Amlodipine administration. The comparisons were made between Day 0 to Day 45, Day 45 to Day 90, and Day 0 to Day 90. The results indicate a significant reduction in both systolic and diastolic blood pressures, except for the comparison between SBP and DBP at Day 45 and Day 90, which showed no statistically significant difference.

**Table 5:** Comparison of Systolic and Diastolic Blood Pressure Changes between Drug Therapy and Placebo Therapy Groups over 90 Days

| | Drug Therapy (mmHg) | Placebo Therapy (mmHg) | p-value |
|---|---|---|---|
| **Systolic Blood Pressure (SBP)** | | | |
| SBP Day 0 | 151.62 ± 13.020 | 150.86 ± 10.396 | 0.672 |
| SBP Day 45 | 137.30 ± 6.519 | 145.43 ± 6.108 | 0.004 |
| SBP Day 90 | 131.89 ± 6.163 | 143.79 ± 6.456 | 0.001 |
| **Diastolic Blood Pressure (DBP)** | | | |
| DBP Day 0 | 94.86 ± 8.035 | 90 ± 7.060 | 0.416 |
| DBP Day 45 | 82.97 ± 5.199 | 86.00 ± 6.945 | 0.041 |
| DBP Day 90 | 81.08 ± 4.585 | 84.86 ± 7.016 | 0.082 |

The Systolic Blood Pressure (SBP) decreased gradually during the two follow-up periods on Day 45 and Day 90 in both treatment groups. The magnitude of the decrease was directly proportional to the duration of treatment, as shown in Table 5. The between-group comparison of SBP percentage on the 45th and 90th day using an Independent-Sample T-test was found to be statistically significant.

The diastolic blood pressure (DBP) has decreased in both treatment groups, and the magnitude of the decrease is directly proportional to the duration of treatment, as indicated in Table 6. The between-group comparison of DBP percent on the 45th day using the Independent-Sample T-test yielded a statistically significant result (p=0.04). However, the between-group comparison of DBP percent on the 90th day using the Independent-Sample T-test did not show statistical significance (p>0.05).

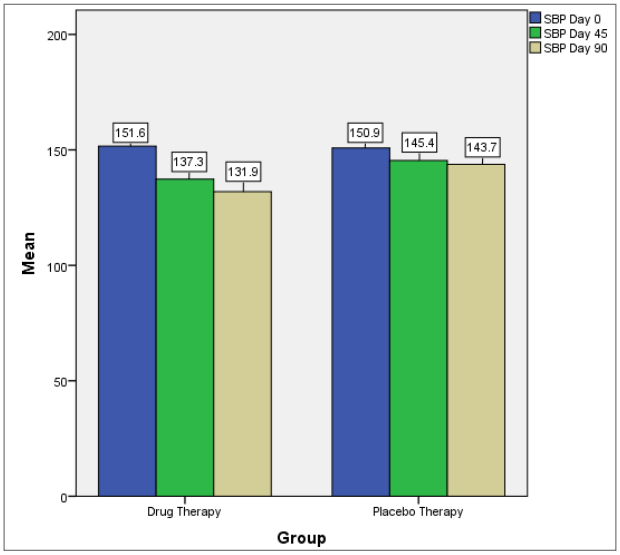


**Figure 6:** Percentage change in SBP relative to baseline (Day 0) in both treatment groups

In order to facilitate the comparison of systolic blood pressure (SBP) among the groups, we expressed SBP as a percentage relative to the baseline measurement taken on Day 0 (set as 100%). Throughout the study period, SBP decreased in all treatment groups, with the lowest values observed at Day 90 for each group. Notably, when comparing the groups, the reduction in SBP was more significant in the group receiving Flax Capsule and equivalent antihypertensive medications, in comparison to the group receiving Placebo Capsule and equivalent antihypertensive medications, as illustrated in Figure 6.

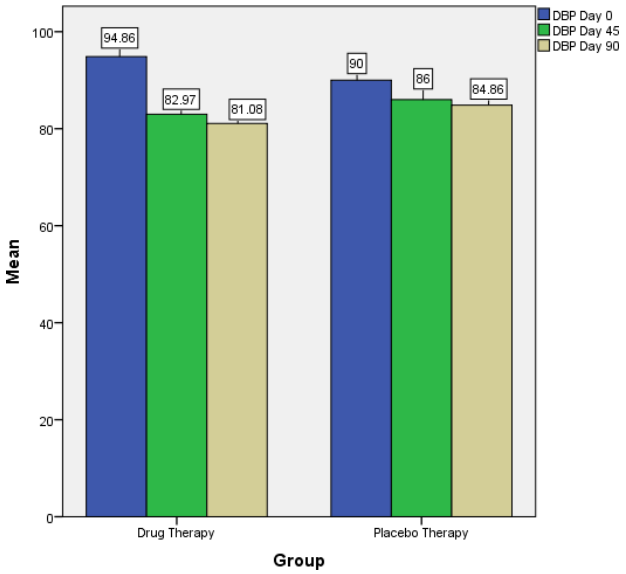


**Figure 7:** Percentage change in DBP relative to baseline (Day 0) in both treatment groups

To standardize the comparison of diastolic blood pressure (DBP) across the groups, we expressed DBP as a percentage relative to the baseline measurement at Day 0 (set as 100%). Over the course of the study, DBP decreased in all treatment groups, reaching its lowest point at Day 90 for each group. However, when comparing the groups, the decrease in DBP was more pronounced in the group receiving Flax Capsule and equivalent anti-hypertensive medications, compared to the group receiving Placebo Capsule and equivalent anti-hypertensive medications, as illustrated in Figure 7.

After 90 days, the flaxseed group demonstrated a significant reduction in mean Systolic Blood Pressure (SBP) from 151.62 to 131.89 mmHg, equating to a 13.01% decrease versus 4.77 % reduction in placebo group (p-value = 0.001). While there was also a reduction in mean Diastolic Blood Pressure (DBP) from 94.86 to 81.08 mmHg, corresponding to a 14.53% decrease in flaxseed group versus 5.7% reduction in placebo group, this change was not statistically significant (p-value = 0.082).

## Discussion

In this study, there were a total of 72 patients, comprising 34 males and 38 females, distributed across different age groups: 18-40 years, 41-60 years, and above 60 years. The mean age of the enrolled patients was 55.38 years, and the mean BMI was 26.53 kg/m$^2$. Among the total cases, 63% fell within the 41-60 years age group, 29% were above 60 years, and only 8% belonged to the 18-40 years age group. Both sexes were equally represented, with females accounting for 53% and males for 47% of the disease occurrence, resulting in a female-to-male ratio of 1.1:1. A study conducted by Levya et al. in Canada in 2013, titled "Potent Antihypertensive Action of Dietary Flaxseed in Hypertensive Patients," is highly

comparable to our study.[11] Their study reported a similar mean age of presentation (67 years) and a male-to-female ratio of 1:1.

The present study aimed to evaluate the effect of Linum usitatissimum L. (Flax) capsules on systolic and diastolic blood pressure in patients taking anti-hypertensive drugs. The study observed that Flax capsules had a beneficial effect on hypertensive patients. The mean systolic and diastolic blood pressure significantly decreased in patients taking Flax capsules and Amlodipine together compared to those taking Placebo capsules and Amlodipine together.

Side effects such as nausea, constipation, and hypotension occurred in 6 patients, and they were appropriately managed at the Medicine OPD. Fortunately, all these patients completed their assigned interventions. Notably, the study conducted by Levya et al. did not address these particular side effects.

Around 80% of the patients were from Sunsari district, while the remaining 20% were from nearby districts. This hospital serves as the tertiary care center for the eastern region of Nepal, explaining the geographical distribution. The religious and ethnic composition of the patients aligned with the regional demographics, with 87% being Hindu, and the remaining 13% comprising Christians, Buddhists, Kiratis, and Muslims.

There was no significant difference in the family history of hypertension among the groups, with 51% reporting a positive family history and 49% reporting a negative family history of hypertension. However, this finding does establish a family history as one of the risk factors for hypertension. Smoking and alcohol consumption were reported by 46% and 50% of the patients, respectively.

Since BMI is significantly correlated with SBP and DBP, the figures demonstrate that approximately 60% of the enrolled patients fell within the obese category, followed by 25% in the overweight category, and around 14-15% within the normal category.

In the case of loss to follow-up, patients were contacted using the contact numbers recorded in the proforma.

In our study, the combination of Flax capsules and anti-hypertensive drugs resulted in a significant reduction ($p<0.05$) in SBP by the 45th day and at the end of the 90th day, compared to the combination of placebo capsules and equivalent anti-hypertensive drugs. The reduction in DBP was significant ($p<0.05$) by the 45th day but became statistically non-significant ($p>0.05$) after the 90th day between the two groups. Approximately 80% of patients from both groups maintained the same dose of anti-hypertensive medication throughout the trial. It has been proposed that Flax capsules lower blood pressure by altering circulating oxylipins through α-linolenic acid-induced inhibition of soluble epoxide hydrolase.[19]

Similarly, various studies have shown the effect of different forms of flax on blood pressure in hypertensive patients. Flaxseed, containing ALA, may exhibit its anti-hypertensive potential through its anti-inflammatory effect. In a randomized, controlled, crossover trial, 23 hyperlipidemic patients were provided with a high-ALA diet, high linoleic acid diet, or a typical western diet for 6-week periods each. The high-ALA diet notably reduced peripheral blood mononuclear cell production of interleukin-6, interleukin-1, and tumor necrosis factor-alpha compared to the high linoleic acid diet.[20] Additionally, ground flaxseed consumption reduced pro-inflammatory oxylipins in the plasma of older adults after 4 weeks.[21] Essential hypertension has been theorized to result from inflammation and endothelial dysfunction, leading to an imbalance between endothelial-derived vasoconstrictive factors and vasodilative factors. If ALA has anti-inflammatory effects, it is likely to prevent the inflammation-induced imbalance of molecules that regulate vascular tone. ALA may also influence inflammation and blood pressure by altering the oxylipin profile.[22]

## Limitations

This research had certain limitations and shortcomings. Firstly, the study was conducted over a relatively short period, which limits our understanding of the long-term effects of flax capsules. A longer duration would have provided more comprehensive insights. Secondly, the sample size was small, restricting the generalizability of the results to larger populations. Including a larger number of participants in future studies would improve statistical power and enhance the validity of the findings. Also, there was unequal distribution of participants based on their gender and religion in both groups, as the sample was selected through randomization during the time of the COVID pandemic. Lastly, the lack of medical staff supervision for the intake of flax capsules raises concerns about consistency and adherence to the prescribed regimen. This may introduce variability and affect the overall effectiveness of the intervention. The quality of the intervention drug could not be measured due to the unavailability of required funds and technologies. Similarly, the effect of flaxseed on lipid profile, blood glucose, and various other inflammatory bio-markers could not be studied due to the limitation of time and funds.

To overcome these limitations, further research is needed. Larger-scale trials with longer durations and closer medical supervision would provide more robust evidence and address the limitations identified in this study.

## Conclusion

Based on observation of our study, the inclusion of flaxseed supplements into the treatment regimen for hypertension, in conjunction with antihypertensive medications, led to a notable reduction in blood pressure levels Based on these findings, it can be concluded that the administration of flax capsules alongside antihypertensive drugs in patients with hypertension can be both effective and safe in maintaining blood pressure levels, consequently reducing the risk of cardiovascular diseases. However, further multicentric randomized clinical trials with greater sample sizes for longer intervention periods and follow-up duration are necessary to estimate effects with precision and negative effects become less likely.

### Abbreviations

ADRs - Adverse Drug Reactions
ALA - Alpha-linolenic acid
BPKIHS - B.P. Koirala Institute of Health Sciences
BMI - Body Mass Index
DBP - Diastolic Blood Pressure
HIV - Human Immunodeficiency Virus
IRC - Institutional Review Committee
ITT - Intention-to-treat
MS - Multiple Sclerosis
NCDs - Non-communicable Diseases
NHRC - Nepal Health Research Council

OPD - Out Patient Department

SBP - Systolic Blood Pressure

SPSS - Statistical Package for the Social Sciences

### Author contributions

Conceptualization: RV.

Methodology: RV, GPR, BK, SS, UC, AS.

Data analysis: RV, RV, PK.

Writing original draft: RV, BS,

Writing review and editing: RV, BS, BK, GPR.

Supervision BS, GPR, SS, BK.

### Conflict of interest

The authors declare no conflict of interest.

### Funding

This study was funded by the principal investigator himself.

### Ethical statement

This research has been approved by the Institutional Review Committee at BPKIHS, Dharan (Reference.no.: - 347/077/078-IRC) and Nepal Health Research Council, Kathmandu-Nepal (Ref.no. - 2608).

### Data availability

The data will be made available by the corresponding author upon reasonable request.

## References

1. World Health Organization. A global brief on hypertension : silent killer, global public health crisis: World Health Day 2013: World Health Organization, ; 2013 [updated 25 June 2013. Available from: 6. https://doi.org/10.1007/978-1-59259-039-1_24 (https://apps.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf)
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603. (https://doi:10.1161/CIR.0000000000000485)
3. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13-e115. (https://doi.org/10.1161/HYP.0000000000000065)
4. Egan BM, Kjeldsen SE, Grassi G, Esler M, Mancia G. The global burden of hypertension exceeds 1.4 billion people: should a systolic blood pressure target below 130 become the universal standard? J Hypertens. 2019;37(6):1148-53. (https://doi:10.1097/HJH.0000000000002021)
5. Stuglin C, Prasad K. Effect of flaxseed consumption on blood pressure, serum lipids, hemopoietic system and liver and kidney enzymes in healthy humans. J Cardiovasc Pharmacol Ther. 2005;10(1):23-7. (https://doi:10.1177/107424840501000103)
6. Adrianne Bendich RJD. Primary and Secondary Preventive Nutrition 2001st ed: Humana; November 29, 2000. (https://doi.org/10.1007/978-1-59259-039-1_24)
7. Dodin S, Cunnane SC, Masse B, Lemay A, Jacques H, Asselin G, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. Nutrition. 2008;24(1):23-30. (https://doi:10.1210/jc.2004-1148)
8. Dodin S, Lemay A, Jacques H, Legare F, Forest JC, Masse B. The effects of flaxseed dietary supplement on lipid profile, bone mineral density, and symptoms in menopausal women: a randomized, double-blind, wheat germ placebo-controlled clinical trial. J Clin Endocrinol Metab. 2005;90(3):1390-7. (https://doi:10.1016/j.nut.2007.09.003)
9. World Health Organization. The Global Health Observatory World Health Organization,; 2022 [Available from: https://doi:10.1155/2016/1656938. (https://doi:10.1155/2016/1656938)
10. Sharma SK, Ghimire A, Radhakrishnan J, Thapa L, Shrestha NR, Paudel N, et al. Prevalence of hypertension, obesity, diabetes, and metabolic syndrome in Nepal. Int J Hypertens. 2011;2011:821971. (https://doi:10.4061/2011/821971)
11. Rodriguez-Leyva D, Weighell W, Edel AL, LaVallee R, Dibrov E, Pinneker R, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. Hypertension. 2013;62(6):1081-9. (https://doi:10.1161/HYPERTENSIONAHA.113.02094 )
12. Burdge GC, Calder PC. Dietary alpha-linolenic acid and health-related outcomes: a metabolic perspective. Nutr Res Rev. 2006;19(1):26-52. (https://doi:10.1079/NRR2005113)
13. Calder PC. n-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. Clin Sci (Lond). 2004;107(1):1-11. (https://doi:10.1042/CS20040119)
14. Tham DM, Gardner CD, Haskell WL. Clinical review 97: Potential health benefits of dietary phytoestrogens: a review of the clinical, epidemiological, and mechanistic evidence. J Clin Endocrinol Metab. 1998;83(7):2223-35. (https://doi:10.1210/jcem.83.7.4752)
15. Kitts DD, Yuan YV, Wijewickreme AN, Thompson LU. Antioxidant activity of the flaxseed lignan secoisolariciresinol diglycoside and its mammalian lignan metabolites enterodiol and enterolactone. Mol Cell Biochem. 1999;202(1-2):91-100. (https://doi:10.1023/a:1007022329660)
16. Basavaraj Madhusudhan. Potential Benefits of Flaxseed in Health and Disease - A Perspective. Agriculturae Conspectus Scientificus (ACS). 2009;74(2). (https://www.researchgate.net/publication/26636227_Potential_Benefits_of_Flaxseed_in_Health_and_Disease_-_A_Perspective)
17. Saman Khalesi RJ, Ismail A,. Flaxseed (Linum usitatissimum L.) consumption and blood thiocyanate concentration in rats. Nutrition & Food Science,. 2012/01/01; 43. (https://www.researchgate.net/publication/262936275_Flaxseed_Linum_usitatissimum_L_consumption_and_blood_thiocyanate_concentration_in_rats)
18. Djousse L, Arnett DK, Pankow JS, Hopkins PN, Province MA, Ellison RC. Dietary linolenic acid is associated with a lower

prevalence of hypertension in the NHLBI Family Heart Study. Hypertension. 2005;45(3):368-73. (https://doi:10.1161/01.HYP.0000154679.41568.e6)

19. Caligiuri SP, Aukema HM, Ravandi A, Guzman R, Dibrov E, Pierce GN. Flaxseed consumption reduces blood pressure in patients with hypertension by altering circulating oxylipins via an alpha-linolenic acid-induced inhibition of soluble epoxide hydrolase. Hypertension. 2014;64(1):53-9. (https://doi:10.1161/HYPERTENSIONAHA.114.03179)

20. Zhao G, Etherton TD, Martin KR, Gillies PJ, West SG, Kris-Etherton PM. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr. 2007;85(2):385-91. (https://doi:10.1093/ajcn/85.2.385)

21. Caligiuri SP, Aukema HM, Ravandi A, Pierce GN. Elevated levels of pro-inflammatory oxylipins in older subjects are normalized by flaxseed consumption. Exp Gerontol. 2014;59:51-7. (https://doi:10.1016/j.exger.2014.04.005)

22. Puddu P, Puddu GM, Zaca F, Muscari A. Endothelial dysfunction in hypertension. Acta Cardiol. 2000;55(4):221-32. (https://doi:10.2143/AC.55.4.2005744)

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Original Article

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# Transesophageal echocardiographic measurement of coronary sinus blood flow to estimate the adequacy of revascularization in patients undergoing coronary artery bypass graft: a prospective observational study

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## Abstract

**Background:** Oxygen supply to the myocardium is determined mainly by the amount of the coronary blood flow. Transesophageal echocardiography is being widely used intraoperatively during cardiac surgery. We studied to compare coronary sinus blood flow using Transesophageal echocardiography before and after coronary artery bypass grafting to determine the adequacy of surgical revascularization in a single cardiac centre in Nepal.

**Methods:** Twenty patients scheduled for elective coronary artery bypass grafting were included in this study. After induction of anesthesia according to institutional protocol, a transesophageal echocardiography probe was inserted into patients' esophagus, and velocity time integral of coronary sinus, coronary sinus diameter, and coronary sinus blood flow per beat at pre-revascularization and post-revascularization periods were recorded.

**Results:** The velocity time integral in the post-revascularization period was significantly higher as compared with the pre-revascularization period (P<0.000). Coronary Sinus diameter in the post-revascularization period was significantly larger as compared with the pre-revascularization period (0.59 vs.0.56 cm) (P<0.000). There was a significant increase in coronary sinus blood flow per beat in the post-revascularization period (4.45±0.66ml) as compared with the pre-revascularization period (4.29±0.65ml) (P<0.000).

**Conclusion:** Transesophageal echocardiography can be used to measure the adequacy of revascularization in CABG patient by measuring the change in real time coronary sinus blood flow before and after revascularization.

**Keywords:** Coronary artery bypass graft, Transesophageal echocardiography, coronary sinus

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## BACKGROUND

Oxygen supply to the myocardium is determined mainly by the amount of the coronary blood flow. In presence of coronary lesions and myocardial ischemia the coronary blood flow decreases so, measurement of the amount of coronary blood flow helps in evaluating the presence of any coronary diseases. Measurement of coronary blood flow can be assessed by coronary sinus blood flow (CSBF). In patients with coronary artery disease, there is reduced CSBF. Any intervention done to increase coronary perfusion may also increase CSBF.

Measurement of CSBF is done by various invasive techniques that require cardiac catheterization using intracoronary Doppler flow wire, thermodilution catheter, or digital coronary angiography. It can also be measured using radioisotope dyes such as argon technique or xenon scintigraphy[1].

Transesophageal echocardiography (TEE) is being widely used intraoperatively during cardiac surgery. Because the echocardiographic probe is located in the esophagus in proximity to the left atrioventricular junction, the TEE can demonstrate

the coronary sinus (CS) with high resolution. Besides this, it can evaluate CSBF in real time with good reproducibility and allows the monitoring of flow before and after the revascularization procedures.

Limited studies has been done using TEE to assess CSBF and see the improvement in coronary artery perfusion after surgical revascularization. The aim of this study is to compare CSBF using TEE before and after coronary artery bypass grafting (CABG) to determine the adequacy of surgical revascularization in a single cardiac centre in Nepal.

## Method

This was a prospective observational study performed at Shahid Gangalal National Heart Center of Nepal. After obtaining Institutional review board approval a written informed consent was obtained from all the patients age above 18 years who were scheduled for elective isolated CABG surgery and not having any of the exclusion criteria (patients' refusal, patient under mechanical ventilator prior to surgery, patients' with ejection fraction <45%, accompanying valvular or other cardiac surgery and emergency Surgery) were enrolled in the study.

Demographic details of the patients were recorded. After the patient was brought to the operation theatre, standard monitoring such as electrocardiography and pulse oximetry were applied. Invasive blood pressure monitoring line and central venous catheter through right internal jugular vein were inserted under standard aseptic precautions. The anesthetic induction was done with midazolam, fentanyl, and propofol as per standard hospital protocol. In all patients, neuromuscular blockade was provided by vecuronium. After anesthetic induction, an appropriatesized (7 for female and 7.5 for male) cuffed high volume low pressure endotracheal tube (ETT-portex, Smiths Medical ASD, INC, USA) was used to secure the airway. Mechanical ventilation was started with volumecontrolled mode with the tidal volume of 8 ml/kg of predicted body weight, respiratory rate of 12 per minute, inspiratory/expiratory ratio 1: 2 and inspiratory oxygen fraction(FiO2) 0.6 with an airoxygen mixture with isoflurane. After that, TEE probe (Philips EpiQ7, USA) was inserted after adequate lubrication and a brief jaw thrust maneuver. Experienced cardiac anesthesiologist inserted the probe and managed all cases. Bite guard was used after TEE probe placement.

By using B-mode echocardiography the image of CS was obtained in modified four chamber view. The pulse doppler sample volume was placed in the CS 1 cm before its inflow in the right atrium. The transducer position was optimized to obtain an angle of less than 40° between the Doppler beam and direction of CSBF. After induction of anesthesia and five minutes after complete revascularization, velocity time integral (VTI) of CS was recorded and diameter of CS was measured by using M-mode. Assuming that the cross-section of CS is elliptical and that the major diameter is double the length of the minor diameter, the cross-section area of CS was calculated as 0.39× diameter of CS[4]. CSBF per beat was then calculated as CS VTI × cross-sectional area of CS. Hemodynamic parameters including heart rate, mean atrial pressure and central venous pressure before and after revascularization were recorded.

Collected data were analysed by means of statistical software SPSS-22. Statistical analysis for demographic variables was done by chi-square test and student's paired t test was applied to compare the mean difference in CS diameter, VTI and CSBF before and after revascularization. P-value of < 0.05 was considered to be statistically significant.

## Results

The demographic data of the patient are as shown in Table 1. The hemodynamic parameters in terms of heart rate and mean arterial pressure though seemed to be changed statistically significantly before and after revascularization, but the range of change was within the acceptable range of 20% of baseline as shown in Table 2. The difference in central venous pressure wasn't statistically significant.

The velocity time integral in the post-revascularization period was significantly higher as compared with the pre-revascularization period (P<0.001). Coronary Sinus diameter in the post-revascularization period was significantly larger as compared with the pre-revascularization period (0.59 vs.0.56 cm) (P<0.001). There was a significant increase in coronary sinus blood flow per beat in the post-revascularization period (4.45±0.66ml) as compared with the pre-revascularization period (4.29±0.65ml) (P<0.001) as shown in Table 3.

Table 1: Demographic data of the patients

| Variables | |
|---|---|
| Sex (M:F) | 11:9 |
| Age(Years) | 62.5(51-76) |
| Weight (kg) | 61(52-88) |
| Height (cm) | 155(145-172) |
| Number of grafts | 3.5(3-5) |

Tables 2: Comparison of Hemodynamic parameters

| | Before revascularization (mean+/- SD) | After revascularization (mean+/- SD) | P value |
|---|---|---|---|
| HR (in mins) | 66.60±7.88 | 73.50±7.48 | 0.001 |
| MAP (mmHg) | 81.70±12.99 | 74.50±5.97 | 0.001 |
| CVP (mmHg) | 13.40±3.08 | 13.70±2.56 | 0.428 |

Tables 3: Comparison of TEE findings

| | Before revascularization (mean+/- SD) | After revascularization (mean+/- SD) | P value |
|---|---|---|---|
| CS VTI (cm) | 14.33±2.18 | 14.82±2.19 | 0.001 |
| CS diameter (cm) | 0.56±0.12 | 0.59±0.12 | 0.001 |
| CSBF per beat(ml) | 4.29±0.65 | 4.45±0.66 | 0.001 |

## DISCUSSION

In CABG various arterial or venous grafts are used in the obstructed vessels in order to increase the coronary artery blood flow. The patency of these graft is the major factor for the success of this surgery. So, proper evaluation of the patency of the graft intra-operatively is very important. Intraoperative assessment tools for

measurement of graft patency include transit time flowmetry and intraoperative fluorescence coronary angiography. However, these measurement modalities aren't available in our center. So, surgeons often use the crude evaluation technique like finger palpation of the graft to assess the patency of graft.

CS drains the venous blood from its tributaries like great cardiac vein, middle cardiac vein, and small cardiac vein. These veins drain the venous blood from the myocardial that is supplied by coronary arteries. Any intervention that aims at restoring the flow of the stenosed vessel increases coronary artery flow that should consequently increase the CSBF. Measurement of CSBF can be used as an indirect tool for the assessment of adequacy of coronary artery perfusion after surgical revascularization[1].

Though measurement of CSBF is done by various invasive techniques that require cardiac catheterization using intracoronary Doppler flow wire, thermodilution catheter, or digital coronary angiography and radioisotope dyes such as argon technique or xenon scintigraphy1-4, but these techniques cannot be used intra-operatively in the operating room. As the use of intraoperative TEE is a routine practice in cardiac surgery, we used TEE to evaluate the change in CSBF after revascularization.

Our study findings showed that the velocity time integral in the post-revascularization period was significantly higher as compared with the pre-revascularization period ($p<0.001$). Coronary Sinus diameter in the post-revascularization period was significantly larger as compared with the pre-revascularization period (0.59 vs.0.56 cm) ($p<0.001$). There was also a significant increase in coronary sinus blood flow per beat in the post-revascularization period (4.45±0.66ml) as compared with the pre-revascularization period (4.29±0.65ml) ($p<0.001$).

In a study done by Meenakshi K et al. to find the change in CSBF after percutaneous coronary angioplasty, they performed transthoracic echocardiography and measured the CS diameter and CSBF. The CSBF per beat increased from 3.06±1.12 to 4.2±1.80 ($p<0.038$) in their study and their result was comparable to our study.

In similar study done by Prajapati M et al. they also found significant improvement in CS diameter (0.68 vs.0.79 cm), CS VTI(16.53 vs 19.66) and CSBF per beat (3.04 vs 4.90) after revascularization in off pump CABG patients. Their findings were also in consistent to our study findings.

Ng DW et al[1]. did transthoracic echocardiography to see the CSBF before and after CABG. They also found significant change in CS VTI from 10.6±1.93 to 13.4±2.3 ($p=0.01$) and significant change in CSBF after revascularization. However, they didn't notice any significant change in CS diameter in their study. The difference noted in CS diameter in our study could be due to the use of retrograde cannula in our study population which could have also contributed in change of the diameter of coronary sinus post revascularization.

In a study done by Hajaghaei M et al. they found CS diameter increased from 8.6 ±1.06 to 9.4±1.21 ($p<0.01$) 1 month after CABG and their findings were also similar to our study findings.

All of our study population didn't develop any complications in the post-operative period and none required intra-aortic balloon pump placement. They were hemodynamically stable throughout their post-operative period and were discharged home with satisfactory outcome.

This study has some limitations, which mainly are related to low number of study patients. In addition, the study was done in on-pump CABG patients with retrograde cannulation in the coronary sinus which could have also contributed in change of the diameter of coronary sinus post revascularization. We also recommend to undergo further studies in off-pump CABG patients as well in the future.

## Conclusion

Transesophageal echocardiography can be used to measure the adequacy of revascularization in CABG patient by measuring the change in real time coronary sinus blood flow pre and post revascularization. So, we recommend to use TEE measurements of CSBF to look for the changes in blood flow after the surgery.

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### Conflict of interest statement:

We declare no perceived or potential conflicts of interest within past 36 months related to this study.

Authors' Contributions: SS Parajuli and RB Adhikari designed the study, took part in acquisition, analysis and interpretation of data, created the initial draft of the manuscript and made critical revisions.

## References

1. Ng DW, Vlachonassios K, Nimalasuriya AR, Nguyen VT, Wijesekera C, Khan A, Chandraratna PA. Usefulness of transthoracic echocardiography in demonstrating coronary blood flow after coronary artery bypass grafting. Am J Cardiol 2004; 93:923–925. Doi: 10.1016/j.amjcard.2003.12.037.
2. Toyota S, Amaki Y. Measurement of coronary sinus flow using transesophageal echocardiography in patients undergoing coronary artery bypass grafting. J Clin Anesth 2000; 12:270–272. Doi: 10.1016/s0952-8180(00)00153-7.
3. Nagaraja PS, Singh NG, Patil TA, Manjunath V, Prasad SR, Jagadeesh AM, Kumar KA. Transesophageal echocardiography estimation of coronary sinus blood flow for the adequacy of revascularization in patients undergoing off-pump coronary artery bypass graft. Ann Card Anaesth 2015; 18:381. Doi: 10.4103/0971-9784.159809.
4. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJ. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971; 44:181–195. Doi: 10.1161/01.cir.44.2.181.
5. Kronzon I, Tunick PA, Jortner R, Drenger B, Katz ES, Bernstein N, et al. Echocardiographic evaluation of the coronary sinus. J Am Soc Echocardiogr 1995; 8:518–26. Doi: 10.1016/s0894-7317(05)80340-2.
6. Illiceto S, Marangelli V, Memmola C, Rizzon P. Transesophageal Doppler echocardiography evaluation of coronary blood velocity in baseline conditions and during dipyridamole induced coronary vasodilatation. Circulation 1991; 83:61–9. Doi: 10.1161/01.cir.83.1.61.
7. Toufan M, Samadikhah J, Alizadeh-Asl A, Azarfarin R, Hakim SH, Yaghoubi A, Farzam S. Measurement of coronary sinus blood flow after first anterior myocardial infarction with

transthoracic echocardiography and its correlation with wall motion scoring index. Saudi Med J 2007; 28:1545–1549. PMID: 17914518

8. Meenakshi K, Swaminathan S, Manickam R. Role of transthoracic echocardiography in the estimation of coronary sinus blood flow in coronary artery disease. Heart Asia 2013; 5:168–171. Doi: 10.1136/heartasia-2013-010346.
9. Prajapati M, Yadav N, Gandhi H, Arora V, Gujja S, Sachan P, Patel S. Measurement of coronary sinus blood flow using transesophageal echocardiography to estimate the adequacy of revascularization in patients undergoing off-pump coronary artery bypass grafting. The Egyptian Journal of Cardiothoracic Anesthesia. 2021 May 1;15(2):48-54. DOI: 10.4103/ejca.ejca_3_21
10. Hajaghaei M, Maleki M, Salehi HR, Ojaghi Z, Noohi F. Coronary flow reserve measurement in the coronary sinus in pre and post CABG status. Iran Cardiovasc Res J 2007; 1:87–89.

Original Article

Nepalese Heart Journal 2024; Vol 21(1), 25-29

# Clinical profile and practice patterns of patients with severe hypercholesterolemia: A Hospital-based registry

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## Abstract

**Background:** Severe hypercholesterolemia, defined as low-density lipoprotein cholesterol of ≥190mg/dL (≥4.9 mmol/L), has a high risk of atherosclerotic cardiovascular disease and premature and recurrent coronary events. Its prevalence may be as high as 5–7% in the general population. This registry aims to provide insights into clinical profiles and practice patterns among such patients treated at the tertiary cardiac hospital of Nepal.

**Methods:** This was a cross-sectional, observational, registry of the patients who were diagnosed with severe hypercholesterolemia from January 2022 to December 2022 in the National Heart Centre.

**Results:** In this registry, 119 cases were included. The mean age of patients was 53 years, with 56.3% being female. Of these patients, 74 (62.1%) were hypertensive, 16 (13.4%) had diabetes mellitus, and 16 (13.4%) used tobacco. A history of premature coronary artery disease was present in 15 (12.6%) patients, and premature peripheral vascular disease in 1 (0.8%) patient. A family history of premature coronary artery disease was reported in 4 (3.3%) patients, and a family history of total cholesterol levels >7.5 mmol/L was present in 20 (16.8%) patients. Tendon xanthoma was found in 4 (3.3%) cases, and arcus cornealis in 22 (18.4%) cases. The body mass index ranged from 15.2 to 43.2, with a mean of 26.3; over 60% of cases were overweight or obese. Rosuvastatin was used in 87 (73.1%) cases, atorvastatin in 32 (26.9%) cases, and ezetimibe 10 mg combined with atorvastatin in 18 (15.1%) cases. High doses of statins were administered in 93 (78.1%) cases.

**Conclusion:** Severe hypercholesterolemia hospital-based registry provides valuable information on severe hypercholesterolemia regarding the associated cardiovascular risk factors and its clinical presentation. Most of the patients were treated with high doses of statins as recommended by guidelines.

**Keywords:** Coronary artery disease; Familial hypercholesterolemia; High intensity statins; Severe Hypercholesterolemia;

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## Introduction

Severe hypercholesterolemia is defined as Low-Density Lipoprotein Cholesterol (LDL-C) of ≥ 190mg/dL (≥ 4.9mmol/L).[1] Prevalence of severe hypercholesterolemia may be as high as 5–7% in the general population.[2,3] Patients with severe hypercholesterolemia have a high risk of Atherosclerotic Cardiovascular Disease (ASCVD) and premature and recurrent coronary events.[4] It is suggested that the risk of coronary artery disease (CAD) is accelerated by 10–20 years in men and 20–30 years in women with LDL-C levels ≥190 mg/dL.[2] The future risk of CAD remains 6-fold higher in those with LDL-C ≥190 mg/dL and no familial hypercholesterolemia-related mutations.[4]

Current guidelines recommend the initiation of high-intensity statin therapy in individuals with LDL-C ≥190 mg/dL without calculating 10-year ASCVD risk, due to their high lifetime risk for ASCVD events that are related to long-term exposure to markedly elevated LDL-C levels.[1,5,6] Initiation of high-intensity statin therapy is strongly recommended in this population to achieve a ≥50% reduction in LDL-C to adequately reduce their risk for future cardiovascular events.[1,7]

There is limited information available about this group of patients in Nepal. This registry aims to provide insights into clinical profiles and practice patterns among severe hypercholesterolemia patients treated at the tertiary cardiac hospital of Nepal.

## Methods

This was a prospective, observational registry done at Shahid Gangalal National Heart Centre (SGNHC), Bansbari, Kathmandu,

Nepal. A web-based performa was designed to collect information about severe hypercholesterolemia patients. Cardiologists were given access to enter the patient's data. Data were entered by the treating cardiologists. All consecutive patients aged >18 years who were diagnosed with severe hypercholesterolemia in the National Heart Center from 2022 January to 2022 December were included. Age, gender, premature CAD in patients (men <55 y old, women <60 y old), premature cerebral or peripheral vascular disease (men <55 y old, women <60 y old), family history of Myocardial Infarction (MI) <50 y old in second-degree relative or <60 y old in first-degree relative, family history of Total Cholesterol (TC) >7.5 mmol/L in a first- or second-degree relative, hypertension, diabetes mellitus, tobacco use, Body Mass Index (BMI), tendon xanthoma and arcus cornealis in patients, total Cholesterol, triglyceride, High density lipoprotein, LDL, treatment received at the time of enrollment were entered in the web-based registry portal.

diabetes mellitus

### Operational definitions are as follows:

Hypertension: Diagnosed case on lifestyle modification or medication

Diabetes Mellitus: Diagnosed case on lifestyle modification or Medication

Family history of premature Coronary artery disease: First-degree relatives who had CAD before 55 years in males and before 65 in Females.

Smoker: Patients were considered as smokers if they report any smoking consumption within the last 1 year of study enrollment.

Tobacco consumer: Patients were considered as Tobacco if they report any tobacco consumption within the last 1 year of study enrollment.

A BMI less than 18.5 was considered underweight, a BMI of 18.5 to <24.9, was considered as healthy weight, a BMI of 25.0 to <30 was considered overweight, BMI of≥30.0 was considered obese.[8]

Data were analyzed using the statistical software, SPSS version 20. Ethical approval for this study was taken from the Institutional Review Committee of SGNHC. Informed written consent after proper counseling regarding the nature and purpose of the study was taken from each respondent.

## Results

During the study period, 119 patients were enrolled in the study. Age ranged from 25 years to 77 years with a mean age of 53 years. Among them 67(56.3%) were female and 52 (43.7%) were males. Among the 119 patients enrolled in this study 74 (62.1%) were hypertensive,16 (13.4%) were Diabetes mellitus patients, and 16(13.4%) patients consumed tobacco. History of premature CAD was diagnosed in 15 (12.6%) patients, a history of premature Peripheral Artery Disease (PAD) in 1(0.8%) patient, a family history of premature CAD was present in 4 (3.3%), and family history of TC>7.5mmol/L was present in 20 (16.8%) patients, Tendon Xanthoma in 4 (3.3%) cases, arcus cornealis in 22 (18.4%) cases as shown in Table 1.

**Table 1.** Baseline characteristic n=119

| Variable | n | % |
|---|---|---|
| Male | 53 | 43.7 |
| Female | 67 | 56.3 |
| Hypertension | 74 | 62.1 |
| DM | 16 | 13.4 |
| Smoking/Tobacco consumer | 16 | 13.4 |
| Premature CAD | 15 | 12.6 |
| Premature PVD | 1 | 0.8 |
| Family History of Premature CAD | 4 | 3.3 |
| Family history of TC>7.5mmol/L | 20 | 16.8 |
| Tendon Xanthoma | 4 | 3.3 |
| Arcus Cornealis | 22 | 18.4 |

BMI ranged from 15.2 to 43.2 with a mean of 26.3. More than 60% of cases were overweight, and obese as shown in Table 2.

**Table 2:** Classification as per BMI

| BMI | n | % |
|---|---|---|
| <18.5 (Underweight) | 4 | 3.3 |
| 18.5-<25 (Normal) | 38 | 31.9 |
| 24.9-<30 (Overweight) | 56 | 47 |
| 30-39.9 (Obese) | 21 | 17.4 |

**Table 3** Lipid profile levels

| | Range | Mean |
|---|---|---|
| TC | 6.3-17.0 | 7.9mmol/L |
| TG | 0.7-5.4 | 1.9mmol/L |
| HDL | 0.8-2.1 | 1.1mmol/L |
| LDL | 4.9-12.7 | 5.8 mmol/L |

Rosuvastatin was used in 87 (73.1%) cases, Dose ranged from 10 to 40mg with a mean of 23.9mg, Atorvastatin in 32 (26.9%) cases, with Dose ranging from 10 mg to 80 mg with a mean of 47.1 mg. Ezetimibe combined with atorvastatin was used in 18(15.1%) cases, in all cases 10 mg of Ezetmibe was used. High-intensity atorvastatin of 40 mg or more was used in 20 (16.8%) cases, Low intensity was used in 12 (10.0%) cases. High-intensity rosuvastatin 20 mg or more was used in 73(61.3%) cases, and Low-intensity rosuvastatin was used in 14 (11.7%) cases. Over 93 (78.1%) cases were treated with high doses of statin as shown in Table 4

**Table 4** Statin and their dose (n=119)

| Statin Dose | Number | % |
|---|---|---|

| | | |
|---|---|---|
| Atorvastatin | 32 | 26.9 |
| 10 | 1 | 0.8 |
| 20 | 2 | 1.6 |
| 30 | 9 | 7.5 |
| 40 | 8 | 6.7 |
| 70 | 9 | 7.5 |
| 80 | 3 | |
| Mean Atorvastation dose | 47.1 mg | |
| Exetimibie+Atovastatin | 18 case | 15.1 |
| Atorvastation 30+10 | 9 | 7.5 |
| Ator 70+10 | 8 | 6.7 |
| Ator 20+10 | 1 | 0.8 |
| Rosuvastatin | 87 | 73.1 |
| 10 | 14 | 11.7 |
| 20 | 49 | 41.1 |
| 40 | 24 | 201 |
| Mean Rosuvastation Dose | 23.9mg | |

## Discussion

Individuals with severe hypercholesterolemia are at significantly increased lifetime risk of CAD. One study involving over 68,000 subjects followed for up to 30 years found that those with LDL-C ≥190 mg/dL had a 2–5 fold increased risk of CAD compared to those with LDL-C <130 mg/dL.[2] Further, CAD occurred 10–20 years earlier in men and 20–30 years earlier in women with LDL-C≥190 mg/dL than in people with LDL-C<130.[9]

In our study patient's ages ranged from 25 years to 77 years with a mean age of 53 years. Among them 67(56.3%) were female and 52 (43.7%) were male. In a study done by Candace L. Jackson, there were 27,963 patients with a recorded LDL-C value. Of these patients, 388 had severe hypercholesterolemia (1.4%). The median age was 57 years, and 66% were women.[9] The exact number of very high LDL patients in Nepal is not known. In a cross-sectional study done on 454 participants by Limbu et al, a cluster sampling method was used through different health camps conducted in Kathmandu valley and found severe hypercholesterolemia in 5.8% of cases.[10] In a study done by Karki et al., fasting lipid profile of 2218 blood samples taken from patients attending a private clinic in Kathmandu found that 26 (1.1%) cases have severe hypercholetraolmia.[11]

In our study family history of TC>7.5mmol/L was present in 16.8% of cases. An important consideration in cases of severe hypercholesterolemia is the potential diagnosis of familial hypercholesterolemia (FH).[11] FH is an autosomal dominant disorder that causes premature CVD due to lifelong elevated LDL-C.[13,14] The heterozygous form of FH is estimated to occur in 1 in 250 to 1 in 500 people, while the incidence of the homozygous form is 1 in 250,000 to 1 in 1 million.[9,15,16] Studies using genetic testing for diagnosis report a 2% prevalence of FH in those with LDL-C 190 mg/dL.[4] An analysis from the NHANES study using clinical criteria reported a 7% prevalence.[17] It is estimated that at least 20 million people with FH worldwide, but 80% are unaware of their diagnosis.[9] The prevalence of FH increases progressively at higher LDL-C thresholds. Both the Simon Broome and AHA diagnostic criteria delineate an LDL-C level above 190 mg/dL as raising the potential for FH, which should then be supported and confirmed by additional clinical criteria.[9] National Lipid Association Guidelines state that an LDL-C 190 mg/dL should raise suspicion for FH and that detailed family history should be collected in all such individuals.[18]

To improve the diagnosis and treatment of FH among severe hypercholesterolemia patients we need to increase awareness. We need to understand current practice regarding the evaluation and management of these patients and apply it in our clinical practice. The 2013 ACC/AHA Cholesterol Guidelines recommended high-intensity statin therapy in all those ages 20 years and older with LDL-C ≥190 mg/dL, without calculation of the estimated 10-year risk of atherosclerotic cardiovascular disease due to their high lifetime risk for ASCVD events that are related to long-term exposure to markedly elevated LDL-C levels.[18] This recommendation was based on extensive data that have demonstrated a benefit in LDL-C reduction, as patients with LDL-C ≥190 mg/dL were excluded from most clinical trials due to their probable need for cholesterol-lowering therapies.[1] In our study all the patients were not treated with high-dose statins. Every effort should be made to treat these patients with high doses of statin. LDL-C reduction ≥50% was recommended as the initial goal, and a potential need for non-statin therapies to achieve optimal LDL-C levels was recognized.[1]

Current guidelines recommend consideration of adding ezetimibe or proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors in high-risk patients, such as those with LDL-C ≥190 mg/dL, who have<50% reduction in LDL-C on maximally tolerated statin therapy.[1] But they were not adequately managed with statins, or other lipid-lowering medications,[9] only a small proportion of those diagnosed receive optimal therapy.[9,19] A study done by Candace L. Jackson showed that 36% of patients with an LDL-C 190 mg/dL had no record of having ever been prescribed a statin.[9] A general practice electronic health record in Australia found that 44% of patients with an LDL-C ≥190 mg/dL had never taken a statin[20] as well and an analysis of statin prescription rates from a national clinical registry showed that 34% of patients with an LDL-C ≥190 mg/dL did not have a statin prescription.[9] Almost 90% of patients had not been prescribed another lipid-lowering medication, such as PCSK9 inhibitors, ezetimibe, niacin, fibrates, or bile acid binding resin, and only 5% were currently on one of these medications.[21] But in our study all the patients were treated with statins, many with high-dose statins. Few of them were treated with ezetimibe. PCSK 9 was not used as it is not available in Nepal. Until PCSK9 inhibitors become available, it is crucial to educate physicians on the importance of using high doses of statins combined with ezetimibe for these patients.

A registry like this can significantly enhance awareness of severe hypercholesterolemia and its management options among both the general public and physicians. These data were collected from the web portal by the treating physicians. The patients included in this study exhibit diverse clinical backgrounds: some underwent general check-ups, others were admitted, and some sought evaluation for additional risk factors such as hypertension and diabetes. There may be variation in the LDL levels as LDL levels were not tested in the same laboratory, different methods of LDL calculation may have been used, and fasting or non-fasting samples were collected. As this was just an observational study, we did not have the effect of different doses of statins, and changes in the LDL level cannot be mentioned.

## In conclusion

The hospital-based registry on severe hypercholesterolemia offers significant insights into the related cardiovascular risk factors, its clinical presentation, and its management. Most of the patients were treated with high doses of statins as recommended by guidelines. Every effort should be made to diagnose and treat these patients.

**Conflicts of interest**

There are no conflicts of interest.

## Reference


1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625.

2. Amanda M. Perak, Hongyan Ning, Sarah D. de Ferranti, MD, MPH, Holly C.Gooding, MD, MSc, John T. Wilkins, MD, MS, and Donald M. Lloyd-Jones, MD.Long-Term Risk of Atherosclerotic Cardiovascular Disease in US Adults With the Familial Hypercholesterolemia Phenotype. Circulation 2016;134:9–19. 10.1161/CIRCULATIONAHA.116.022335

3. Abul-Husn NS, Manickam K, Jones LK, Wright EA, Hartzel DN, Gonzaga-Jauregui C, O'Dushlaine C, Leader JB, Lester Kirchner H, Lindbuchler DM, Barr ML, Giovanni MA, Ritchie MD, Overton JD, Reid JG, Metpally RP, Wardeh AH, Borecki IB, Yancopoulos GD, Baras A, Shuldiner AR, Gottesman O, Ledbetter DH, Carey DJ, Dewey FE, Murray MF. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. Science. 2016; 23:354(6319):aaf7000. doi: 10.1126/science.aaf7000.

4. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, van Leeuwen EM, Natarajan P, Emdin CA, Bick AG, Morrison AC, Brody JA, Gupta N, Nomura A, Kessler T, Duga S, Bis JC, van Duijn CM, Cupples LA, Psaty B, Rader DJ, Danesh J, Schunkert H, McPherson R, Farrall M, Watkins H, Lander E, Wilson JG, Correa A, Boerwinkle E, Merlini PA, Ardissino D, Saleheen D, Gabriel S, Kathiresan S. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. Journal of the American College of Cardiology. 2016;67:2578–2589. doi: 10.1016/j.jacc.2016.03.520

5. T R Pedersen, J Kjekshus, K Berg, T Haghfelt, O Faergeman, G Faergeman, K Pyörälä, T Miettinen, L Wilhelmsen, A G Olsson, H Wedel; Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–1389. doi:10.1016/j.atherosclerosissup.2004.08.027

6. Kashef MA, Giugliano G. Legacy effect of statins: 20-year follow up of the West of Scotland Coronary Prevention Study (WOSCOPS). Global cardiology science practice. 2016;2016:e201635. doi: 10.21542/gcsp.2016.35

7. Antonio J Vallejo-Vaz , Michele Robertson , Alberico L Catapano , Gerald F Watts , John J Kastelein , Chris J Packard , Ian Ford , Kausik K Ray . Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up. Circulation 2017;136(20):1878-1891. doi:https://doi.org/10.1161/CIRCULATIONAHA.117.027966

8. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998;6 Suppl 2:51S–209S.

9. Candace L. Jackson, Zahid Ahmad, Sandeep R. Das, Amit Khera.The evaluation and management of patients with LDL-C 190 mg/dL in a large health care system. American Journal of Preventive Cardiology 1 (2020) 100002. doi:https://doi.org/10.1016/j.ajpc.2020.100002

10. YR Limbu,SK Rai, K Ono,M Kurokawa,J-I Yanagida,G Rai, N Gurung,CK Rai. Lipid profile of adult Nepalese population. Nepal Med Coll J 2008; 10(1): 4-7. PMID: 18700621

11. Karki DB, Neopane A, Pradhan B, Magar A.Lipid levels in Nepalese population. Kathmandu University Medical Journal 2004) 2(4): 349-353. PMID: 16388248

12. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation 2015;132(22):2167–92. doi: 10.1161/CIR.0000000000000297

13. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5(3 Suppl): S1–8. doi: 10.1016/j.jacl.2011.04.003

14. Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolemia. Atherosclerosis 2003; 168(1):1–14.doi: 10.1016/s0021-9150(02)00330-1

15. Langslet G, Ose L. Screening methods in the diagnosis and assessment of children and adolescents with familial hypercholesterolemia. Expert Rev Cardiovasc Ther 2013;11(8):1061–6.doi: 10.1586/14779072.2013.814851

16. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States national health and Nutrition Examination Surveys (NHANES). Circulation 2016; 133(11):1067–72.doi: 10.1161/CIRCULATIONAHA.115.018791

17. Bucholz EM, Rodday AM, Kolor K, Khoury MJ, de Ferranti SD. Prevalence and predictors of cholesterol screening, awareness, and statin treatment among US adults with familial hypercholesterolemia or other forms of severe dyslipidemia

(1999-2014). Circulation 2018;137(21):2218–30.doi: 10.1161/CIRCULATIONAHA.117.032321

18. Neil J. Stone,Jennifer G. Robinson,Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel,Anne C. Goldberg,David Gordon,Daniel Levy, Donald M. Lloyd-Jones,et al.2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–S45.doi:https://doi.org/10.1161/01.cir.0000437738.63853.7a
19. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation: executive summary. J Atheroscler Thromb 2014;21(4):368–74.doi: 10.1016/j.ijcard.2013.11.025
20. Vickery AW, Ryan J, Pang J, Garton-Smith J, Watts GF. Increasing the detection of familial hypercholesterolemia using general practice electronic databases. Heart Lung Circ 2017;26(5):450–4.doi: 10.1016/j.hlc.2016.09.012
21. Al-Kindi SG, DeCicco A, Longenecker CT, Dalton J, Simon DI, Zidar DA. Rate of statin prescription in younger patients with severe dyslipidemia. JAMA Cardiol 2017;2(4):451–2. doi:10.1001/jamacardio.2016.5162

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Original Article

Nepalese Heart Journal 2024; Vol 21(1), 31-36

# Our experience with cardiac MRI in a tertiary health care center in Nepal

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## Abstract

**Background and Aim:** Cardiac Magnetic Resonance (CMR) is a crucial noninvasive imaging technique for the thorough evaluation of the heart in various cardiovascular conditions. The potential to offer quantitative data on cardiac perfusion and function make CMR an exceptional choice of imaging for providing functional and morphological information about the heart. We performed cardiac MR evaluation of patients over a period of 12 months. Our aim was to establish the common cardiac MR indications and the diagnoses in different age groups in our population.

**Method:** A retrospective analysis of patients undergoing CMR at Shahid Gangalal National Heart Center, Kathmandu, Nepal over a period of 12 months, from October 2021 to September 2022 was done. All patients who underwent cardiac MRI at our center, irrespective of age, sex, and indication were included in the study. A total number of 392 patients were included in our study who had undergone Cardiac MRI on a 3Tesla platform at our center. The respective protocols, tailored to the disease being investigated, were followed based on the indication of each patient. Data were entered in a predesigned proforma and SPSS was used for the analysis.

**Results:** The most common indication to perform CMR at our centre was found to be the myocardial viability test. Among 147 patients (37.5 % of the study population) assessed for myocardial viability, 120 (81.6 %) showed infarction in the left anterior descending (LAD) territory, 17 (11.5 %) showed infarction in the LCX territory and 10 (6.8 %) showed RCA territory infarction. The most common cardiomyopathy diagnosed with cardiac MRI at our center was hypertrophic cardiomyopathy (HCM) (15.5 %), followed by dilated cardiomyopathy (DCM) (10.0 %). Other various cardiac MR diagnoses of patients were congenital heart disease (CHD) (5.8 %), arrhythmogenic right ventricular cardiomyopathy (ARVC) (5.6 %), myocarditis (3.0 %), valvular heart disease (VHD) (3.0 %), cardiac mass/pseudo mass (2.0 %), pericarditis (1.7 %), and others (3.3 %). 48 patients that represented about 12.2 % of the total study population who underwent cardiac MRI at our centre had normal CMR findings.

**Conclusion:** Cardiac MRI is an excellent imaging modality in the evaluation of different groups of cardiovascular diseases. It does not only provide the diagnosis but also helps in evaluating the prognostic parameters in different cardiac patients. Hence, the use of CMR is encouraged in clinical practice in our setting to implement early and appropriate therapies in cardiac patients that may ultimately improve patient outcomes.

**Keywords:** Cardiac Magnetic Resonance (CMR), Viability, Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM), Myocarditis, Arrhythmogenic right ventricular cardiomyopathy (ARVC), Congenital heart disease (CHD)

**DOI:** https://doi.org/10.3126/nhj.v21i1.65648

## Introduction

Magnetic resonance (MR) imaging, one of the several available radiologic modalities, is acknowledged as a promising noninvasive imaging technique with an improved spatial and temporal resolution, and an absence of ionizing radiation[1]. Cardiac Magnetic Resonance (CMR) is a crucial noninvasive imaging technique for the thorough evaluation of the heart in various cardiovascular pathologies including viability evaluation, cardiomyopathies, pericardial pathologies and congenital anomalies of the heart[1,2]. The potential to offer quantitative data on cardiac viability, perfusion, and function make CMR an exceptional choice of imaging where the functional and morphological information of the heart can be evaluated through cine images that facilitate quantifying end-diastolic and end-systolic volumes[1]. In addition, CMR is helpful in

the diagnosis of valvular diseases and acquired conditions such as cardiac lesions and masses including metastases. The basic cardiac MRI sequences may generally be divided into bright-blood and black-blood sequences. The bright blood sequence is a gradient echo (GRE) based acquisition that gathers data on cardiac function and blood flow. Bright blood imaging is utilized to assess both segmental and global left ventricular (LV) function which is represented by the high signal intensity of rapidly flowing blood. This sequence aids in the measurements of blood flow, LV mass, myocardial perfusion, and coronary morphology. Black blood sequence is a spin echo (SE) based acquisition that depicts fast-moving blood as having low signal intensity. This sequence primarily aids to characterize cardiac wall, pericardium and the mediastinal anatomy. Delayed gadolinium enhancement (DGE) is another valuable sequence in which gadolinium is used as a contrast agent and delayed enhancement offers relevant information based on the specific cardiac condition, such as in the detection of myocardial viability, myocardial fibrosis, and so on. As a result, the DGE sequence is acknowledged as the gold standard imaging approach for ischemic and nonischemic cardiomyopathies[1]. Hence, CMR imaging is the decisive and gold standard mode of imaging technique in a wide range of cardiac conditions. The principal objective of this study was to establish the common cardiac MR indications in our setting and the CMR diagnoses in different age groups in our Nepalese population.

## Methods

Our study was a retrospective analysis of patients undergoing CMR at Shahid Gangalal National Heart Center over a period of 12 months, from 1st October, 2021 to 30th September, 2022. All patients who underwent cardiac MRI at our centre in our 3Tesla MR platform were included in the study. Following the ethical approval of the Institutional Review Board, the data of the patients were obtained retrospectively. A total number of 392 patients were included in our study who had performed Cardiac MRI at our centre. The CMR sequences including the black blood and the bright blood images were carried out in all the patients. The short-tau inversion recovery (STIR) images were obtained from the base to the apex of the heart in the short-axis view. The delayed gadolinium enhancement (DGE) phase-sensitive inversion recovery (PSIR) sequences were obtained in short-axis, four-chamber, and vertical long-axis views. The respective protocols were followed based on the indication of each patient undergoing CMR.

### CMR features for diagnosis

For the myocardial viability test, three principal protocols were evaluated: wall motion using cine gradient echo, resting perfusion by first-pass contrast-enhanced studies, and infarction/scar by delayed gadolinium-enhanced inversion recovery imaging. All coronary artery territories were analyzed, and the affected coronary arteries and infarcted segments were localized based on the varying extent of delayed GAD enhancement in the myocardium. Bull's eye diagram was given illustrating the viable and the non-viable segments in different territories.

For the evaluation of cardiomyopathies, the ventricular volumes were evaluated along with the wall thickness, ventricular systolic function (ejection fraction), and myocardial mass. We used the diagnostic parameter of the maximal left ventricular wall thickness of ≥15 mm in the end-diastolic phase in conjunction with left ventricular outflow (LVOT) obstruction plus with or without systolic anterior motion (SAM) of the mitral valve to diagnosis hypertrophic cardiomyopathy (HCM). In the diagnosis of dilated cardiomyopathy (DCM), ventricular dilatation associated with thinning of the ventricular wall along with the left ventricular ejection fraction was assessed. To diagnose infiltrative cardiomyopathies, T2/STIR images were examined for the presence of inflammation and edema and delayed GAD images for the scar tissue or fibrosis. The characteristic CMR features to diagnose amyloidosis used were concentric, symmetric or asymmetric thickening of the left ventricle wall, difficulty in nullifying the myocardium, elevated native T1 time and extracellular volume (ECV), disproportionate atrial enlargement with diffuse, subendocardial, or patchy enhancement patterns in LGE sequences. The non-compaction cardiomyopathy was assessed based on the ratio of noncompacted to compacted myocardium where the threshold of a ratio above 2.3, measured at end-diastole, was used.

The modified Lake Louise criteria were followed for the diagnosis of acute myocarditis wherein the myocardial edema was identified by a visible regional high T2 signal intensity on the STIR sequence. Patchy / diffuse subepicardial or mid myocardial delayed GAD enhancement was identified in these patients that represented the retention of contrast agents in the affected myocardial tissue.

The modified task force criteria were followed in the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). Right ventricular dyssynchronous motion along with reduced RVEF were assess to diagnose ARVC in patients with arrhythmia.

Acute and chronic pericarditis were diagnosed based on the pericardial thickness of ≥4 mm, depicted as a dark, low signal intensity pericardium (usually associated with significant fibrocalcific changes). The post-contrast studies were assessed for the presence of pericardial inflammation and pericardial scar shown by early and late enhancement respectively.

The stack of steady-state fast precession (SSFP) cine images of the whole thorax were used in the evaluation of CHDs. Both the vascular and valvular flow were assessed, shunts were quantified, and left as well as right ventricular myocardial function was measured.

Data were then entered in a predesigned proforma, and SPSS was applied to do the analysis.

## Results

### Study population

Out of 392 patients, 269 (68.6%) were male with age ranging from 8 to 82, and 123 (31.4%) were female with age ranging from 13 to 86 (Figure 1). The most common age group of patients referred to us for the CMR evaluation was between 51 to 60 years of age. This represented 24.5% of our study population (Figure 2).

### CMR indications and diagnoses

The most common indication to perform cardiac MRI at our centre was for viability evaluation, comprising of 37.5% of the study population (147 cases). Among the patients evaluated for viability, 114 (77.5%) were male and 33 (22.4%) were female. Among 147 patients (37.5% of the study population) assessed for myocardial viability, 120 (81.6%) showed infarction in the left anterior descending (LAD) territory, 17 (11.5%) showed infarction in the left circumflex artery (LCX) territory and 10 (6.8%) showed infarction in the right coronary artery (RCA) territory. The most common cardiomyopathy diagnosed with cardiac MRI at our

center was hypertrophic cardiomyopathy (HCM) which comprised of 61 cases (15.5%) followed by dilated cardiomyopathy (DCM) comprising of 39 cases (10.0%). Other cardiac MR diagnoses of patients were 23 (5.8%) of congenital heart disease (CHD), 22 (5.6%) arrhythmogenic right ventricular cardiomyopathy (ARVC), 12 (3.0%) valvular heart disease (VHD), 12 (3.0%) myocarditis, 8 (2.0%) cardiac mass/pseudo mass, 7 (1.7%) pericarditis and 13 (3.3%) others. About 48 (12.2%) number of patients who underwent cardiac MRI had normal CMR findings (Table 1) (Figure 3). In patients diagnosed with HCM, the most common variant was septal form of hypertrophic cardiomyopathy 27 cases (44.2%), followed by concentric form 26 cases (42.6%), apical 6 (9.8%), and basal 2 (3.2%). Out of 39 (10.0%) cases of DCM, 27 (69.2%) were ischemic and 12 (30.7%) were non-ischemic DCM. Among various congenital diseases, Ebstein's anomaly 17 (73.9%) was found to be the most common indication for cardiac MRI at our center followed by follow-up cases of tetralogy of fallot (TOF). We had 8 cases of cardiac masses in this time period who came to us for CMR evaluation. Among the 8 cases, 50% were diagnosed to have pseudomass or thrombus by CMR. Cardiac pseudo-masses seen included right atrial appendage thrombus, caseous calcification of mitral annulus (CCMA), and LV cavity apical thrombus. There were 7 cases of pericarditis representing 1.7% of the study population. Few miscellaneous conditions were grouped in other categories, which included iron overload cardiomyopathy, ventricular non compaction and subendocardial fibroelastosis amongst others (Table 1, Figure 3).

**Table 1.** Number of patients based on CMR diagnosis

| S.N | CMR Diagnosis | Number of patients (%) |
|---|---|---|
| 1. | Viability | 147 (37.5) |
| | **a. Left anterior descending (LAD) territory infarction** | 120 (81.6) |
| | **b. Left circumflex artery (LCX) territory infarction** | 17 (11.5) |
| | **c. Right Coronary Artery (RCA) territory infarction** | 10 (6.8) |
| 2. | Hypertrophic Cardiomyopathy (HCM) | 61 (15.5) |
| | **a. Septal** | 27 (44.2) |
| | **b. Concentric** | 26 (42.6) |
| | **c. Apical** | 6 (9.8) |
| | **c. Basal** | 2 (3.2) |
| 3. | Dilated Cardiomyopathy (DCM) | 39 (10.0) |
| | **a. Ischemic** | 27 (69.2) |
| | **b. Non-ischemic DCM** | 12 (30.7) |
| 4. | Congenital Heart Disease (CHD) | 23 (5.8) |
| | **a. Ebstein's anomaly** | 17 (73.9) |
| | **b. Tetralogy of fallot (TOF)** | 2 (8.6) |
| | **c. Transposition of great arteries (TGA)** | 2 (8.6) |
| | **d. Total anomalous pulmonary venous connection (TAPVC )** | 1 (4.3) |
| | **e. Ventricular septal defect (VSD)** | 1 (4.3) |
| 5. | Arrhythmogenic right ventricular cardiomyopathy (ARVC) | 22 (5.6) |
| 6. | Myocarditis | 12 (3.0) |
| 7. | Valvular Heart Disease (VHD) | 12 (3.0) |
| 8. | Cardiac mass/Pseudomass | 8 (2.0) |
| | **a. Metastases** | 2 (25) |
| | **b. Cardiac mass** | 2 (25) |
| | **c. Pseudomass** | 4 (50) |
| | • **Right atrial appendage thrombus** | 1 (25.0) |
| | • **Caseous calcification of mitral annulus (CCMA)** | 1 (25.0) |
| | • **LV cavity thrombus** | 2 (50.0) |
| 9. | Pericarditis | 7 (1.7) |
| 10. | Others | 13 (3.3) |
| | **a. Infiltrative cardiomyopathy** | 5 (1.3) |
| | **b. Amyloidosis** | 3 (0.8) |
| | **c. Non-compaction cardiomyopathy** | 2 (0.5) |
| | **d. Iron overload** | 1 (0.2) |
| | **e. Subendocardial fibroelastosis** | 1 (0.2) |
| | **f. Pericarditis** | 1 (0.2) |
| 11. | Normal | 48 (12.2) |

## Discussion

There are numerous causes of chest pain and the timely recognition of the etiology is of utmost importance as treatment and prognosis vary among different conditions. In spite of the availability of several modern therapeutic options, up to one-third of individuals with acute myocardial infarction (MI) experience clinical heart failure, which continues to be a common and major healthcare burden[3,4]. Following an MI, the detection of viable myocardium has significant implications to predict the possible advantages of revascularization. CMR with a good spatial resolution has been established as the gold standard for evaluating viability based on the presence and pattern of DGE that estimates myocardial scar. A viability assessment using CMR can offer crucial diagnosis and prognosis in cases of complicated coronary disease with simultaneous left ventricular (LV) dysfunction[5,6]. In acute care, CMR has the role to rule out inconclusive diagnoses, evaluate risk stratification for patients with coronary artery disease, and identify the risk of future cardiac events such as reinfarction or heart failure. As per the American Heart Association's guidelines, CMR may be an alternative method to examine patients planned for conventional percutaneous coronary intervention. Similarly, the European Society of Cardiology encourages non-invasive screening in patients suspected of having acute coronary syndrome but with negative cardiac biomarkers and normal or ambiguous electrocardiographic changes. In such circumstances, CMR may meet the key objective of excluding causes of acute chest pain in addition to identifying inconclusive clinical diagnoses[3,7,8].

Based on gender predilection, males are at higher risk of suffering ischemic heart disease as shown by previous studies which is consistent with the result in our study. The age distribution revealed the prevalence of the disease increases with advancing age[9,10]. The

leading causes behind male predominance could be the lifestyle factors such as smoking, unhealthy eating habits, obesity, and social stress amongst others. Therefore, on a positive note, appropriate precautions if taken may lower the likelihood of developing ischemic heart disease. Overall, CMR can play a crucial role as an essential modality of choice to evaluate myocardial viability that can guide in management by assisting to decide the revascularization of the diseased vessel.

In the present study, 48 patients which represent about 12.2% of the study population showed normal CMR findings. Most of those cases were sent for the evaluation of unexplained arrhythmias. Few of the patients were sent with the suspicion of acute myocarditis. However, none of them showed definite arrhythmogenic foci or features of myocarditis as edema and delayed GAD enhancement. Ventricular arrhythmias may occur in patients with different structural heart diseases such as cardiomyopathies, chronic myocarditis, and healed myocardial infarction or they can be idiopathic in origin. It is essential to timely recognize ventricular arrhythmias related to cardiac causes from idiopathic ones as myocardial structural abnormalities carry the risk of causing sudden cardiac death. CMR with tissue characterization techniques can aid in the identification and characterization of the arrhythmogenic substrate in individuals with ventricular arrhythmias. Furthermore, previous studies have revealed that arrhythmia is frequently seen in men at around the age of 40, which is consistent with our findings in the form of ARVC[11,12]. Normal CMR findings in few of the arrhythmia patients might be related to the idiopathic arrhythmias.

The fact that HCM was frequently found among men in our study is supported by previous studies on HCM that have consistently revealed a male predominance[13,14]. The findings of young individuals usually having HCM with frequent involvement of interventricular septum are also consistent with earlier research[15,16,17]. Besides gender and age predilection, the extraordinary temporal and spatial resolution, features like tissue characterization, and the capacity to image in any desired tissue plane make CMR a crucial imaging tool guiding not only in the diagnosis but also in evaluation of the prognostic parameters[17].

In every 1000 newborns, congenital heart disease (CHD) is seen in about 6-8 cases. Early diagnosis and treatment have improved the survival rate of CHD patients making them through to adulthood[18]. However, there are still a certain number of the adult population with CHD, who go unnoticed and present late. The role of CMR imaging is constantly growing in evaluating congenital heart diseases in both pediatric and adult patients due to its non-invasiveness and lack of ionizing radiation. Moreover, CMR has emerged as a tool of imaging for CHD patients who have had surgical repairs and require a lifelong follow-up in order to monitor interval changes allowing for serial comparisons without the need of being exposed to radiation[19]. Hence, by providing accurate ventricular volume, function, arterial flow, information on regurgitation, and three-dimensional contrast angiography providing additional anatomical information plus late gadolinium sequences characterizing several pathologies, CMR is the preferred imaging technique to assess any possible CHD patients including the follow-up cases of post-surgical intervention. We had limited evaluation of congenital heart diseases in the pediatric population because of unavailability of all the required MR compatible instruments and pediatric anesthesia set ups in our MR system.

Therefore, in the clinical scenario of our center (which largely represents the scenario of the whole country), we have found CMR to be an efficient imaging modality to aid both in the diagnosis and management of patients of different cardiac conditions.

## Limitations:

This study however has some limitations. The prolonged scan time required for the imaging and the patient's ability to follow breath-holding commands led to artifacts in few of the studies thus necessitating further processing during image acquisition. Secondly, considering the fact that CMR has only recently been introduced and practiced in Nepal, this study is a pioneering effort to gather data on the prevalent cardiac conditions encountered in a national cardiac center of Nepal. There are no other centers yet in our country where the CMR is regularly practiced. This is only a single-centered study done over a period of one year. A multicenter study in a larger population is warranted in the future to have a more precise understanding of the different cardiac conditions prevalent in our Nepalese population.

## Conclusion

In conclusion, we found CMR to be an excellent imaging modality in the evaluation of different groups of cardiovascular diseases. The various methodologies of CMR such as cine-CMR to examine the morphology and function of the heart, and contrast-enhanced CMR to detect myocardial infarctions and characterize tissue non-invasively make it a unique tool that can be used alone or in combination with other imaging modalities for proper diagnosis and treatment. It does not only provide the diagnosis but also helps in evaluating the prognostic parameters in different cardiac patients. Hence, the use of CMR is encouraged in clinical practice to implement early and appropriate therapies that may ultimately improve patient outcomes.

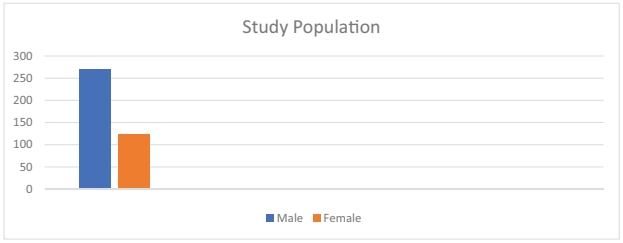


*Figure 1. Distribution of the study population according to gender*

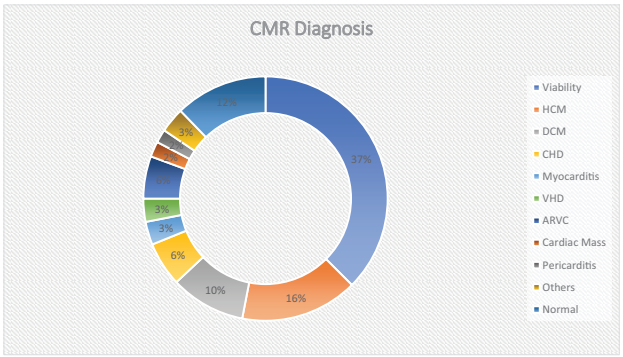


*Figure 2. Distribution of the study population according to age*

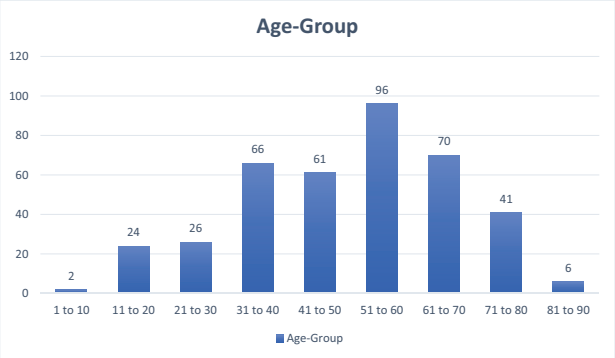


*Figure 3. Distribution of the study population according to CMR diagnosis*

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## Conflict of interests

Dr Marisha Aryal, Executive Editor of Nepalese Heart Journal did not participate in the editorial process of this article.

## References:

1. Saeed M, Van TA, Krug R, Hetts SW, Wilson MW. Cardiac MR imaging: current status and future direction. Cardiovasc Diagn Ther. 2015 Aug;5(4):290-310. DOI: 10.3978/j.issn.2223-3652.2015.06.07.PMID:26331113;PMCID:PMC4536478.

2. Leiner T, Strijkers G. Advances in cardiovascular MR imaging. MAGMA. 2018 Feb;31(1):3-6. DOI: 10.1007/s10334-018-0676-x. PMID: 29411168.

3. Broncano J, Bhalla S, Caro P, Hidalgo A, Vargas D, Williamson E, Gutiérrez F, Luna A. Cardiac MRI in Patients with Acute Chest Pain. Radiographics. 2021 Jan-Feb;41(1):8-31. DOI: 10.1148/rg.2021200084. Epub 2020 Dec 18. PMID: 33337967.

4. Garcia MJ, Kwong RY, Scherrer-Crosbie M, Taub CC, Blankstein R, Lima J, Bonow RO, Eshtehardi P, Bois JP; American Heart Association Council on Cardiovascular Radiology and Intervention and Council on Clinical Cardiology. State of the Art: Imaging for Myocardial Viability: A Scientific Statement From the American Heart Association. Circ Cardiovasc Imaging. 2020 Jul;13(7):e000053. DOI: 10.1161/HCI.0000000000000053. Epub 2020 Jul 13. PMID: 32833510.

5. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000 Nov 16;343(20):1445-53. DOI: 10.1056/NEJM200011163432003. PMID: 11078769.

6. Al-Sabeq B, Nabi F, Shah DJ. Assessment of myocardial viability by cardiac MRI. Curr Opin Cardiol. 2019 Sep;34(5):502-509. DOI: 10.1097/HCO.0000000000000656. PMID: 31394561; PMCID: PMC7546497.

7. Gibler WB, Cannon CP, Blomkalns AL, Char DM, Drew BJ, Hollander JE, Jaffe AS, Jesse RL, Newby LK, Ohman EM, Peterson ED, Pollack CV; American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care); Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group; Society of Chest Pain Centers. Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: a scientific statement from the American Heart Association Council on Clinical Cardiology (Subcommittee on Acute Cardiac Care), Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration With the Society of Chest Pain Centers. Circulation. 2005 May 24;111(20):2699-710. DOI: 10.1161/01.CIR.0000165556.44271.BE. PMID: 15911720.

8. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007 Jul;28(13):1598-660. DOI: 10.1093/eurheartj/ehm161. Epub 2007 Jun 14. PMID: 17569677.

9. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, Alblooshi FMK, Almatrooshi MEAH, Alzaabi MEH, Al Darmaki RS, Lootah SNAH. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. Cureus. 2020 Jul 23;12(7):e9349. DOI: 10.7759/cureus.9349. PMID: 32742886; PMCID: PMC7384703.

10. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980-2009. Eur Heart J. 2013 Oct;34(39):3017-27. DOI: 10.1093/eurheartj/eht159. Epub 2013 Jun 25. PMID: 23801825; PMCID: PMC3796269.

11. Muser D, Santangeli P, Selvanayagam JB, Nucifora G. Role of Cardiac Magnetic Resonance Imaging in Patients with Idiopathic Ventricular Arrhythmias. Curr Cardiol Rev. 2019;15(1):12-23. doi: 10.2174/1573403X14666180925095923. PMID: 30251607; PMCID: PMC6367696.

12. Nucifora G, Muser D, Masci PG, Barison A, Rebellato L, Piccoli G, Daleffe E, Toniolo M, Zanuttini D, Facchin D, Lombardi M, Proclemer A. Prevalence and prognostic value of concealed structural abnormalities in patients with apparently idiopathic ventricular arrhythmias of left versus right ventricular origin: a magnetic resonance imaging study. Circ Arrhythm Electrophysiol. 2014 Jun;7(3):456-62. doi: 10.1161/CIRCEP.113.001172. Epub 2014 Apr 25. PMID: 24771543.

13. Siontis KC, Ommen SR, Geske JB. Sex, Survival, and Cardiomyopathy: Differences Between Men and Women With Hypertrophic Cardiomyopathy. J Am Heart Assoc. 2019 Nov 5;8(21):e014448. DOI: 10.1161/JAHA.119.014448. Epub 2019 Oct 30. PMID: 31663428; PMCID: PMC6898853.

14. Trongtorsak A, Polpichai N, Thangjui S, Kewcharoen J, Yodsuwan R, Devkota A, Friedman HJ, Estrada AQ. Gender-Related Differences in Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis. Pulse (Basel). 2021 Aug 2;9(1-2):38-46. DOI: 10.1159/000517618. PMID: 34722354; PMCID: PMC8527921.

15. Amano Y, Kitamura M, Takano H, Yanagisawa F, Tachi M, Suzuki Y, Kumita S, Takayama M. Cardiac MR Imaging

of Hypertrophic Cardiomyopathy: Techniques, Findings, and Clinical Relevance. Magn Reson Med Sci. 2018 Apr 10;17(2):120-131. DOI: 10.2463/mrms.rev.2017-0145. Epub 2018 Jan 18. PMID: 29343659; PMCID: PMC5891337.

16. Hansen MW, Merchant N. MRI of hypertrophic cardiomyopathy: part I, MRI appearances. AJR Am J Roentgenol. 2007 Dec;189(6):1335-43. DOI: 10.2214/AJR.07.2286. PMID: 18029869.

17. Morgan RB, Kwong R. Role of Cardiac MRI in the Assessment of Cardiomyopathy. Curr Treat Options Cardiovasc Med. 2015 Nov;17(11):53. doi: 10.1007/s11936-015-0410-1. PMID: 26446716.

18. Ntsinjana HN, Hughes ML, Taylor AM. The role of cardiovascular magnetic resonance in pediatric congenital heart disease. J Cardiovasc Magn Reson. 2011 Sep 21;13(1):51. DOI: 10.1186/1532-429X-13-51. PMID: 21936913; PMCID: PMC3210092.

19. Partington SL, Valente AM. Cardiac magnetic resonance in adults with congenital heart disease. Methodist Debakey Cardiovasc J. 2013 Jul-Sep;9(3):156-62. doi: 10.14797/mdcj-9-3-156. PMID: 24066199; PMCID: PMC3782323.

Original Article

Nepalese Heart Journal 2024; Vol 21(1), 37-42

# Frequency of multi-vessel disease and its association with N Terminal-Pro Brain Natriuretic Peptide Levels among patients with First ST-Elevation Myocardial Infarction.

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## Abstract

**Background and Aims:** To determine the frequency of multi-vessel disease among patients with First ST-Elevation Myocardial Infarction and to identify the cutoff value of N Terminal-Pro Brain Natriuretic Peptide (NT-proBNP) for diagnosis of multi-vessel disease.

**Methodology:** A descriptive cross-sectional study was conducted in the Department of Cardiology at a tertiary care hospital from September 2021 to February 2022. The study included 150 patients who presented to the emergency room with first ST-elevation myocardial infarction and preserved ejection fraction. NT-proBNP levels were tested within 12 hours of hospital admission. The severity of coronary artery disease was assessed by the number of vessels affected labeled, the luminal diameter narrowing and the syntax score.

**Results:** The mean age of participants was 60.60±11.1 years. 76% were men, 53.3% of the participants had hypertension, 44% had type 2 diabetes, and 14% were smokers. The mean BMI of the patients was 27.86±3.86. The mean ejection fraction of the patients was 50±4.5.Single-vessel disease was present in 47 (31%) and 103 (69%) had multi-vessel disease. The mean NT-proBNP level in single-vessel disease was 561.34 pg/mL, and in multi-vessel disease, it was 1640.65 pg/mL. Raised levels of NT-proBNP were significantly associated with the severity of coronary artery disease. (P-value <0.05). The optimal cut-off value of NTpro-BNP for ruling out multiple vessel disease was 947.50 pg/mL at 81% of sensitivity.

**Conclusion:** Pro-BNP is a valuable biomarker in assessing the severity of coronary artery disease in STEMI patients. Its levels have been shown to correlate with the degree of CAD severity including multi-vessel involvement.

**Keywords:** Acute Coronary Syndrome, NT-proBNP, coronary artery disease.

**DOI:** https://doi.org/ 10.3126/nhj.v21i1.65664

## Introduction

Inadequate blood and oxygen supply to the myocardium due to coronary artery stenosis generates a demand-supply imbalance and is the most common cause of myocardial ischemia in coronary artery disease (CAD). Blood flow is restricted by the formation of an atherosclerotic plaque in the coronary artery lumen.[1]

NT-proBNP, Troponin I, and Hs-CRP (High-sensitivity C-reactive Protein) are the three most well-known cardiac biomarkers related to the severity of coronary artery disease.[2] The neurohormone N terminal pro-B-type natriuretic peptide (NT-proBNP), which is elevated in acute myocardial infarction and angina pectoris, is synthesized and released by ventricular muscles.[3] The two basic sources of BNP and NT-proBNP release are wall stress and myocyte stretch. Among its various activities are sympathetic nerve activation, natriuresis, vasodilation, and inhibition of the renin-angiotensin-aldosterone system.[4]

BNP and NT proBNP have been shown to offer predictive information on acute coronary syndrome (ACS)[5], and they seem to be associated to the severity of CAD in these patients and have demonstrated an association with multivessel disease, poor TIMI flow, as well as are markers of coronary disease extension.[6]

Despite the worldwide use of NT-proBNP testing, prospective data that examine its role in the diagnosis of multivessel disease in ACS has been limited in our population.[7] So, we planned this

study to determine the prevalence of multi-vessel disease among patients with First ST-Elevation Myocardial Infarction as well as to determine NT-ProBrain Natriuretic Peptide cut-off value for the diagnosis of multi-vessel disease.

## Materials and Method:

This descriptive cross-sectional study enrolled 150 consecutive patients, who presented to the emergency department with STEMI and underwent coronary artery angiography and primary angioplasty, for a period of six months from September 2021 - February 2022. The NT-proBNP levels were sent along with the baseline labs in the emergency department along with Troponin I and limited echocardiography was done to evaluate wall motion abnormality, left ventricular morphology, and systolic function pre-intervention and complete echocardiography (including diastolic dysfunction and RV systolic dysfunction) was done post-intervention, Those with preserved ejection fraction were then included in the study and those with reduced ejection fraction , more than grade 1 diastolic dysfunction and RV systolic dysfunction were excluded from the study. The hospital's ethical committee approved the research and informed consent was taken from the patients.

The inclusion criteria included both genders, male, and female, >18 years who presented to the emergency room with their first case of STEMI, which is indicated by a typical ST segment elevation >1mm in at least 2 or more contiguous leads accompanied by a characteristic chest pain lasting for more than 20 minutes.

When blood levels of cardiac troponin (cTn) rise above the 99th percentile upper reference limit (URL), myocardial damage is considered to be present. The injury may be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL, or chronic, in the setting of persistently elevated cTn levels.[8]All patients who had a prior history of cardiomyopathy, renal failure, surgical history ( having cardiopulmonary bypass) or having any valve surgery or any valvular disease, and those with a previous history of acute myocardial infarction, patients with left main disease and cardiogenic shock, electrocardiograms with pre-existing bundle branch block or displaying non-sinus rhythm and poor quality echocardiographic images were excluded from the study.

The levels of NT-proBNP were measured using an automated electrochemiluminescence immunoassay (ECLIA) on an Analyzer Axym from Abbott Diagnostic in line with established methods. The detection range of the test was 5-25,000 pg/ml, with a normal value of 194 pg/ml. The transthoracic echocardiogram was done using (GE Vivid 95), and the left ventricular ejection fraction was estimated using the modified biplane method.[9] The severity of coronary artery disease was assessed in multiple ways. First in terms of the number of vessels affected labeled as single vessel when one major coronary artery was involved and multi-vessel when ≥2 major coronary vessels were involved. According to the luminal diameter narrowing, ≥50% for the left main coronary artery and 70% for the major coronary arteries, also only those vessels were considered which had a diameter of ≥ 1.5mm.[10] Apart from this, the angiograms were also scored according to the syntax score system. For this, two interventional cardiologists were taken on board who were blinded to the patient characteristics and the study protocol. A senior cardiologist's opinion was sought when there was a discrepancy between the two results and then a consensus was reached. For the purpose of calculation, the software on the following website (http://www.syntaxscore.com) was used. Only coronary arteries with a diameter of 1.5mm having lesions causing ≥ 50% of stenosis were included in the calculation. According to the syntax score the patients were divided into 3 tertiles as follows; a low syntax group with a score of ≤22, an intermediate group with a score between 23 to 32, and a high syntax group with a score of ≥ 33 [11].

## Sample size calculation and Data analysis

The sample size was calculated through Sample Size Calculator by Wan Nor Arifin (Available at https://wnarifin.github.io/ssc/ss1prop.html) by taking the prevalence of multivessel disease= 54%[12], margin of error=8%. The total calculated sample size was 150 patients. The statistical analysis of the collected data was carried out by using IBM SPSS Statistics version 26. Mean and standard deviation was computed for quantitative variables. Frequency and percentages were reported for qualitative variables. ANOVA was applied for mean comparison while the chi-square/Fisher exact test was applied to check the association of qualitative variables. Pearson's correlation coefficient was applied to determine the relationship between quantitative variables. The level of significance was considered at $p<0.05$.

Result: Among 150 participants, 76% (n=114) were men. The patients included had a mean age of 60.60 ± 11.1 years. Out of the total patients, 53.3% (n=80) were hypertensive whereas 44% (n=66) were diabetic and 14% (n=21) were smokers. Details of all demographics are mentioned in Table 1. Regarding the involvement of CAD, 31% (n=47) and 69% (n=103) patients had single-vessel disease and multi-vessel disease, respectively. The Association of CAD with demographics and risk factors are presented in Table 2. Troponin I (p=0.000) and NTpro-BNP (p=0.000) were significantly associated with the severity of coronary artery disease. The mean syntax score was 17.36 ± 3.5 for for single-vessel disease and 26.53 ± 5.2 was for multi-vessel disease.

The mean pro-BNP was 561.34 pg. /ml in single-vessel disease and 1640.65 pg/ml in multi-vessel disease. The Pro BNP and Syntax score showed a moderate, positive, and statistically significant relationship (r= 0.66, P <0.001) as presented in Figure 1. The optimal cut-off value of NTpro-BNP for ruling out multiple vessel disease was 947.50 pg/mL at 81% of sensitivity. The area under the receiver operating characteristic curve (ROC) of PRO BNP for diagnosing diagnosis of multi-vessel disease was 0.93 at 95% confidence interval (Figure 2).

Other predictive values for cut-off with different levels of sensitivity and specificity are mentioned in the table. 3.

**Table 1:** Patients' history and demographics

| Patient's characteristics | frequency (percent) |
|---|---|
| Age(years); mean± std. dev | 60.6 ± 11.1 |
| Groups | |
| ≤40 years | 7(4.7) |
| 41-59 years | 61(40.7) |

| | |
|---|---|
| ≥60 years | 82(54.7) |
| Gender | |
| Male | 114(76) |
| Female | 36(24) |
| Trop-I (ng/mL); mean± std. dev | 9.81±7.97 |
| Groups | |
| <0.30 ng/mL | 23(15.3) |
| 0.30-10 ng/mL | 72(48) |
| 10-25 ng/mL | 38(25.3) |
| >25 ng/mL | 17(11.3) |
| Co-morbidities | |
| Hypertension | |
| Yes | 80(53.3) |
| No | 70(46.7) |
| Diabetes Mellitus | |
| Yes | 66(44) |
| No | 84(56) |
| Smoking Status | |
| Smoker | 21(14) |
| Non-Smoker | 129(86) |
| Type of MI | |
| Anterior | 115(76.7) |
| Antero-lateral or lateral | 15(10) |
| Inferior | 20(13.3) |
| Coronary artery disease | |
| Single vessel disease | 47(31.3) |
| Multi vessel disease | 103(68.7) |

**Table 2:** Association of CAD Severity with Demographic and Risk Factors

| Patient's characteristics | Coronary artery disease frequency (percent) | | p-value |
|---|---|---|---|
| | Single | Multi Vessel | |
| **Age** | | | |
| ≤40 years | 3(6.4) | 4(3.9) | 0.661 |
| 41-59 years | 20(42.6) | 41(39.8) | |
| ≥60 years | 24(51.1) | 58(56.3) | |
| **Gender** | | | |
| Male | 37(78.7) | 77(74.8) | 0.598 |
| Female | 10(21.3) | 26(25.2) | |
| **Troponin-I** | | | |
| <0.30 ng/mL | 18(38.3) | 5(4.9) | <0.001* |
| 0.30-10 ng/mL | 16(34) | 56(54.4) | |
| 10-25 ng/mL | 4(8.5) | 34(33) | |
| >25 ng/mL | 9(19.1) | 8(7.8) | |
| NT Pro BNP | | | |
| <450 pg. /ml | 17(36.2) | 4(3.9) | <0.001* |
| 450-1000 pg. /ml | 11(23.4) | 25(24.3) | |
| >1000 pg. /ml | 19(40.4) | 74(71.8) | |
| Co-morbidities | | | |
| **Hypertension** | | | |
| Yes | 21(44.7) | 59(57.3) | 0.151 |
| No | 26(55.3) | 44(42.7) | |
| **Diabetes Mellitus** | | | |
| Yes | 20(42.6) | 46(44.7) | 0.809 |
| No | 27(57.4) | 57(55.3) | |
| **Smoking Status** | | | |
| Smoker | 3(6.4) | 18(17.5) | 0.069 |
| Non-Smoker | 44(93.6) | 85(82.5) | |
| **Type of MI** | | | |
| Anterior | 32(68.1) | 83(80.6) | 0.225 |
| Antero-lateral or lateral | 6(12.6) | 9(8.7) | |
| Inferior | 9(19.1) | 11(10.7) | |

*Chi-square/fisher exact test was applied.*
**Significant at 0.05 level.*

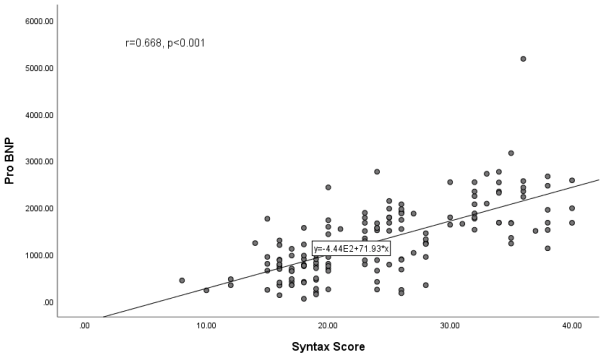


*Figure.1. Relationship between Pro BNP and Syntax Score*

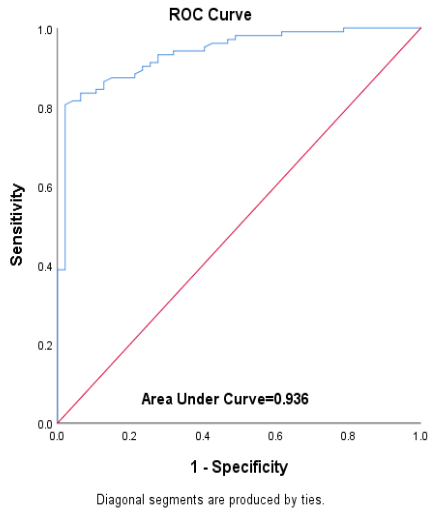


*Figure.2. ROC Curve for detection of Pro BNP cut-off in diagnosis of multi vessel disease*

**Table No 3:** ROC Coordinates of the Curve of different Pro-BNP cutoffs for diagnosis of multi-vessel disease

| Coordinates of the Curve | | |
|---|---|---|
| **Positive if Greater Than or Equal To** | **Sensitivity** | **1 - Specificity** |
| 947.5000 | .816 | .064 |
| 962.0000 | .816 | .043 |
| 981.5000 | .806 | .021 |

## Discussion:

The primary finding of the current study was that patients who presented with their first ST elevation myocardial infarction were more likely to have multi-vessel disease (68.7 %). Patients with low NT-proBNP values had single-vessel disease, whereas those with high NT-proBNP values had multivessel coronary artery disease. Early assessment at presentation in the emergency room helps with the stratification of risk in patients suffering from acute myocardial infarction as it is a critical predictor of outcome in these patients.[13] Another study reported that BNP and NT-proBNP are related to long-term prognosis in patients with predominant ST-segment elevation AMI.[14] A few studies have found that BNP levels in persons suffering from ACS can correlate with the CAD severity, degree as well as TIMI flow.[15]

When pro-BNP levels increase, it relates to a worsening of coronary artery disease. This is shown in one of the well-known studies, BIOMARCS.[16] when the left anterior descending artery is obstructed, Pro-BNP levels are greater than when the left circumflex and right coronary arteries have stenotic lesions. These elevated levels of Pro-BNP indicate multi-vessel involvement of the coronaries.[16] when a patient has an acute myocardial infarction, blood levels of natriuretic peptides (atrial natriuretic peptide, NT-ProBNP, and BNP) rise dramatically. 16 According to the findings of this investigation, the plasma NT-ProBNP level may be used to assess the degree of myocardial ischemia.[16] BNP levels are elevated in STEMI patients, unstable angina patients, and cases of myocardial infarction with non-ST elevation, displaying the extent of the severity of coronary vascular disease and aberrant coronary blood flow.[17] However, with respect to the cited study, our study was characterized by the absence of left ventricular dysfunction and enlargement, which are the main factors responsible for BNP increase.[18]

According to the findings of a meta-analysis, patients with acute coronary syndrome who had elevated BNP levels had an increased chance of dying or having a myocardial infarction.[19] Additionally, there is a notable rise in the likelihood of unfavorable consequences.[19] Another study showed that higher NT-proBNP levels were associated with cardiovascular and all-cause mortality in an unselected, large population of elderly patients in the primary care setting, independent of traditional risk factors, implying that NT-proBNP can help identify subjects at high risk for cardiac events.[20] Subjects with greater levels of NT-proBNP had a higher incidence of all-cause and cardiovascular mortality.[20] Another study explored in more depth and found Participants with stage 1 hypertension with elevated NT-proBNP had a higher risk of heart disease than those with stage 2 hypertension with lower NT-proBNP.[21] Similarly one more researcher found that NT-proBNP could predict worse outcomes in dysglycemic individuals with Chronic Coronary Syndrome and normal LVSF, implying that NT-proBNP could aid in risk stratification in this population.[22] The above studies differ from the present study as we did not control risk factors.

There are certain limitations of this study. It was an observational study with a small sample size and single center therefore, it is difficult to interpret concrete conclusions, also comprehensive echocardiography was not done prior to intervention. Further studies should be conducted in this regard to determine the sensitivity and specificity of NT-pro-BNP in predicting single and multi-vessel disease.

## Conclusion:

The findings of this study support the utilization of Pro-BNP as a valuable marker in the risk stratification of patients with first ST–elevation myocardial infarction to assess the severity of coronary artery disease. Pro-BNP levels have been shown to correlate with the degree of CAD severity including multi-vessel involvement and can provide important prognostic information. Further research and validation studies are warranted to confirm the clinical utility of Pro-BNP in guiding optimal treatment strategies for STEMI patients.

**Conflict of interest**

The authors declared no conflict of interest.

**Funding disclosure**

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## References:

1. Poznyak AV, Litvinova L, Poggio P, Moschetta D, Sukhorukov VN, Orekhov AN. From diabetes to atherosclerosis: Potential of metformin for management of cardiovascular disease. Int J Mol Sci 2022;23(17):9738. https://doi.org/10.3390/ijms23179738
2. Tasar O, Kocabay G, Cagdas M, Karabag Y. Correlation of B-type natriuretic peptide with severity of coronary artery disease assessed by SYNTAX score ii in ST elevation acute coronary syndrome patients. Intl J Cardiovas Acad. 2019;5(4):129. https://doi.org/10.4103/IJCA.IJCA_36_19
3. Diao Y, Yin M, Zhang B, Sun B. Predictive value of N-terminal pro-B-type natriuretic peptide (NT-pro BNP) combined with D-dimer for no-reflow phenomenon in patients with acute coronary syndrome after emergency of percutaneous coronary intervention. Bioengineered. 2021;12(1):8614-21. https://doi.org/10.1080/21655979.2021.1988361
4. Zhu Y, He H, Qiu H, Shen G, Wang Z, Li W. Prognostic Value of Systemic Immune-Inflammation Index and NT-proBNP in Patients with Acute ST-Elevation Myocardial Infarction. Clinical Interventions in Aging. 2023:397-407. https://doi.org/10.2147/CIA.S397614
5. Artha IM, Bakta IM, Manuaba IB, Wita IW, Rohman MS, Astawa IN, et al. The Effects of Percutaneous Coronary Intervention on Biomarkers and Quality of Life in Patients With Chronic Total Coronary Artery Obstruction. Cardiol Res. 2023;14(1):69-78. https://doi.org/10.14740/cr1455
6. Sarak T, Karadeniz M. The relationship between serum NT-proBNP levels and severity of coronary artery disease assessed by SYNTAX score in patients with acute myocardial infarction. Turk J Med Sci. 2019;49(5):1366-73. https://doi.org/10.3906/sag-1902-26
7. Goyal BM, Sharma SM, Walia M. B-type natriuretic peptide levels predict extent and severity of coronary artery disease in non-ST elevation acute coronary syndrome and normal left ventricular function. Indian heart J. 2014;66(2):183-7. https://doi.org/10.1016/j.ihj.2013.12.015
8. Thygesen K. What's new in the fourth universal definition of myocardial infarction? Circ. 2018; 138:e618–e651. https://doi.org/10.1161.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Euro. Heart J.Cardiovasc.Imaging. 2015 Mar 1; 16(3):233-71. https://doi.org/10.1093/ehjci/jev014
10. Xiong QF, Fu XR, Ku LZ, Zhou D, Guo SP, Zhang WS. Diagnostic performance of coronary computed tomography angiography stenosis score for coronary stenosis. BMC Medical Imaging. 2024 Feb 9; 24(1):39.
11. Ho AB, Tran QB, bao Tran Q. The Role of N-Terminal-Pro-B-Type Natriuretic Peptide (NT-proBNP) and High-Sensitivity Troponin T (Hs-Troponin T) in the Evaluation of the Syntax Score in Patients With Acute Coronary Syndrome. Cureus. 2024 Mar 6; 16(3). DOI: 10.7759/cureus.55653
12) Varani E, Balducelli M, Aquilina M, Vecchi G, Hussien MN, Frassineti V, et al Single or multivessel percutaneous coronary intervention in ST-elevation myocardial infarction patients. Catheter Cardio Inte. 2008;72(7):927-33. https://doi.org/10.1002/ccd.21722
13) Zhang C, Jiang L, Xu L, Tian J, Liu J, Zhao X,wt al., Implications of N-terminal pro-B-type natriuretic peptide in patients with three-vessel disease. Eur Heart J. 2019;40(41):3397-405. https://doi.org/10.1093/eurheartj/ehz394
14) Tamara AF, Altoukhy S, AbdelHamid I. The Predictive Value of Estimation of N Terminal-Pro B-Type Natriuretic Peptide in Patients with ST Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention for the Outcome of Myocardial Reperfusion. The Egyptian J Hosp Med. 2023;90(1):1831-7. https://doi.org/10.21608/ejhm.2023.284343
15) Benmachiche M, Marques-Vidal P, Waeber G, Mean M. In-hospital mortality is associated with high NT-proBNP level. PLoS One. 2018; 13(11):e0207118. https://doi.org/10.1371/journal.pone.0207118
16) Oemrawsingh RM, Akkerhuis KM, de Mulder M, Umans VA, Kietselaer B, Schotborgh C, et al., High-Frequency Biomarker Measurements of Troponin, NT-proBNP, and C-Reactive Protein for Prediction of New Coronary Events After Acute Coronary Syndrome: BIOMArCS Study. Circ 2019;139(1):134-6. https://doi.org/10.1161/CIRCULATIONAHA.118.036349
17) Rudolf H, Mügge A, Trampisch HJ, Scharnagl H, März W, Kara K. NT-proBNP for risk prediction of cardiovascular events and all-cause mortality: The getABI-study. IJC Heart Vasc. 2020;29:100553. https://doi.org/10.1016/j.ijcha.2020.100553
18) Richards AM. N-terminal B-type natriuretic peptide in heart failure. Heart fail clin. 2018;14(1):27-39. https://doi.org/10.1016/j.hfc.2017.08.004
19) Fangauf SV, Belnap BH, Meyer T, Albus C, Binder L, Deter HC, et al. Associations of NT-proBNP and parameters of mental health in depressed coronary artery disease patients. Psychoneuroendocrinology. 2018;96:188-94. https://doi.org/10.1016/j.psyneuen.2018.06.001
20) Rudolf H, Mügge A, Trampisch HJ, Scharnagl H, März W, Kara K. NT-proBNP for risk prediction of cardiovascular events and all-cause mortality: The getABI-study. IJC Heart Vasc. 2020;29:100553. https://doi.org/10.1016/j.ijcha.2020.100553

21) Hussain A, Sun W, Deswal A, de Lemos JA, McEvoy JW, Hoogeveen RC, et al. Association of NT-ProBNP, blood pressure, and cardiovascular events: the ARIC study. J Am Coll Cardiol. 2021; 77(5):559-71. https://doi.org/10.1016/j.jacc.2020.11.063

22) Liu HH, Cao YX, Jin JL, Guo YL, Zhu CG, Wu NQ, et al. Prognostic value of NT-proBNP in patients with chronic coronary syndrome and normal left ventricular systolic function according to glucose status: a prospective cohort study. Cardiovasc Diabeto. 2021;20(1):84. https://doi.org/10.1186/s12933-021-01271-0

Original Article

Nepalese Heart Journal 2024; Vol 21(1), 43-48

# Accuracy of Electrocardiography Criteria for Left Ventricular Hypertrophy in Hypertensive Patients at Shahid Gangalal National Heart Centre

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## Abstract

**Background:** Hypertension is the leading cause of cardiovascular disease and premature death worldwide. Left ventricular hypertrophy (LVH), a measure of hypertensive target organ damage in the heart is associated with increased morbidity, mortality and development of arrhythmias. This study was designed to identify the more accurate ECG criteria for identifying LVH taking LVH by echocardiography as reference.

**Methods:** A cross sectional study was conducted at Shahid Gangalal National Heart Centre. A total of 252 patients were included. A 12-lead ECG and Echocardiography were done. Analysis done by SPSS 25. Stata-14 software was used for ROC (Receiver operating characteristics) comparison and P<0.05 considered statistically significant.

**Results:** Sensitivity, specificity, PPV, NPV and accuracy of Sokolow-Lyon criteria in diagnosis LVH was 41.8%, 80.8%, 67.1%, 59.7% and 61.9% respectively. The results of the test parameters taking Cornell Voltage criteria to detect LVH was 65.6%, 73.1%, 69.6% 69.3% and 69.4%. Likewise, the test parameters of cornell voltage duration measurement was 57.4%, 84.6%, 77.8%, 67.9% and 71.4% respectively. Similarly results of the test parameters by Romhilt-Estes system was 36.9%, 88.5%, 75%, 59.9% and 63.5% respectively. Area under the curve(AUC) of Sokolow-Lyon index, Cornell voltage criteria, Cornell voltage duration measurement and Romhilt- Estes system was 0.613, 0.693, 0.71 and 0.627 respectively.

**Conclusion:** In our study Cornell Voltage duration measurement criteria had a higher sensitivity and higher AUC to detect LVH. The different ECG criteria must be integrated with the clinical scenario. Isolated interpretation of LVH using a single ECG criteria has a low diagnostic value.

**Keywords:** left ventricular hypertrophy, Sokolow-Lyon, Cornell Voltage, Romhilt-Estes point score

**DOI:** https://doi.org/10.3126/nhj.v21i1.65968

## Introduction

Hypertension is the leading cause of cardiovascular disease and premature death worldwide.[1] Hypertension affects 1 billion worldwide and it remains the most common, readily identifiable, and reversible risk factor for myocardial infarction (MI), stroke, heart failure, atrial fibrillation, aortic dissection, peripheral arterial disease, and cognitive decline.[2] Left ventricular hypertrophy (LVH), a measure of hypertensive target organ damage in the heart, has been reported to be associated with increased morbidity and mortality and development of atrial arrhythmias.[3,4]

The presence of left ventricular hypertrophy, in addition to hypertension, thus has important implications for assessing risk and managing patients, including decisions on interventions other than antihypertensive treatment, such as lipid lowering treatment and life-style modifications.[5]

ECG LVH also provides unique prognostic information for increased risk of SCD, even when adjusted for echocardiographic LVH.[6] Electrocardiography (ECG) and echocardiography (ECHO) can be applied to detect LVH in clinical practice. The diagnosis of LVH should preferably be made by ECHO because

it can visually measure every parameter of cardiac structure in a noninvasive method.[7] The greater convenience and lower cost of the ECG continue to support its widespread use for the diagnosis of ventricular hypertrophy in clinical practice, epidemiological studies, and clinical trials.

Several ECG criteria, such as the Sokolow–Lyon index, Cornell voltage or Cornell voltage duration product, and RavL are available to assess LVH. Most of previous studies have been conducted in Caucasians and the diagnostic performance of ECG criteria for Asians remains under investigation.[8,9] We believe that this study will aid in identifying the more accurate ECG criteria for identifying LVH taking LVH by echocardiography as reference and will help in identifying, assessing risk and managing such patients.

## OBJECTIVES

To compare four different ECG criteria's of left ventricular hypertrophy in terms of diagnostic accuracy taking echocardiographically diagnosed left ventricular hypertrophy as reference standard.

## OPERATIONAL DEFINITION

**Hypertension:** Hypertension be diagnosed when a person's systolic blood pressure (SBP) in the office or clinicis≥140mmHg and/or their diastolic blood pressure (DBP) is ≥90mmHg following repeated examination in accordance with the methods and guidelines provided by the internationals society of hypertension[10] or patients taking anti- hypertensive medications for more than 6 months.

**Left Ventricular Hypertrophy:** LVH as defined by echocardiographic or electrocardiographic criteria. Electrocardiographically Sokolow-Lyon index, Cornell voltage criterion, Cornell voltage duration measurement and Romhilt-Estes point score system was applied to diagnose LVH. LVH is diagnosed as

1. Sokolow-Lyonindex-SV1+RV5>3.5mVorRaVL>1.1mV
2. Cornell voltage criterion - SV3 + RaVL > 2.8 mV in males and > 2.0 mV in females
3. Cornell voltage duration measurement- Cornellvoltage × QRS duration > 2436 mm-sec
4. Romhilt-Estes point score system

Any limb lead R wave or S wave >2mV (3 points)

SV1 or SV2 ≥ 3.0 mV (3 points)

RV5 to RV6 ≥ 3.0 mV (3 points)

ST-T wave abnormality, no digitalis therapy (3 points)

ST-T wave abnormality, digitalis therapy (1 point)

Left atrial abnormality (3 points)

Left axis deviation ≥ −30 degrees (2 points)

QRS duration ≥ 90 m sec (1 point)

Intrinsicoid deflection in V 5 or V 6 ≥ 50 msec (1 point)

Points of 5 or more was taken as LVH.

**Echocardiographically** LVH is diagnosed as LVM/BSA > 95 g/m2 in females and > 115 g/m2 in males and LVM/ height > 51 g/m2 in males and > 47 g/m2 in females according to the European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) recommendations.[11]

**Obesity:** Obesity is defined as abnormal or excessive fat accumulation that may impair health. Western Pacific Regional Office of WHO (WPRO) defined as overweight (BMI 23.0–24.9) and obesity (BMI ≥25.0) for Asian populations.[12]

The formula to calculate BMI = kg/m2 where kg is a person's weight in kilograms and m2 is their height in metres squared.

**Smoking Status**-As defined by CDC.

**Current smoker**-An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes every day or some days.

**Former smoker**- An adult who has smoked at least 100 cigarettes in his or her lifetime but who currently do not smoke.

**Never smokers**- An adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime.

## MATERIALS AND METHODS

**Setting:** Cardiology Department of Shahid Gangalal National Heart Centre, Kathmandu, Nepal.

**Duration of the study**: - 6 months from August 2021 to February 2022.

**Sample size:** 252

Calculated using Dr. Lin Naing calculator.

**Sample selection**

**Inclusion criteria**

1. All the patients presenting to the OPD diagnosed with hypertension or under anti-hypertensive medications irrespective of the presenting complain or duration of therapy.
2. Patient'sageshouldbefrom 35-65 years of age.
3. Patients willing to take part with consent in the study.

**Exclusion criteria**

1. Patients with cardiomyopathies.
2. Patients with valvular heart diseases.
3. Patients with left/right bundle branch block
4. Patients with left anterior fascicular block
5. Patients with valvular heart diseases
6. Patients with any underlying kidney disease
7. Patients with other secondary causes of hypertension
8. Patients with gestational hypertension or pre-eclampsia.
9. Patients unwilling to participate

## STUDY DESIGN: Cross sectional study

Following the ethical clearance from the Institutional Review Board (IRB) of the Shahid Gangalal National Heart Centre, a cross sectional study was conducted. Cases diagnosed with hypertension or under anti- hypertensive medications and fulfilling the inclusion criteria was enrolled as cases. They were explained about the purpose of the study and the methods used. Informed written consent was taken in either Nepali or English language whichever they feel comfortable assuring full confidentiality. All patients underwent full history taking and physical examination. A 12-lead resting ECG was recorded at 25 mm/s and 1 mV/cm standardization. The 12-lead

ECG was read by two independent cardiologists and findings were recorded.

Defined electrocardiographic indices was applied to diagnose LVH. Echocardiography was done by using GE healthcare Vivid E95 echocardiography machine.

Echocardiographic measurement performed by the investigator measuring inter ventricular septum (IVS), left ventricular internal diameter (LVID), and posterior wall thickness (PWT) and left ventricular mass (LVM) was calculated using the American Society of Echocardiography (ASE) recommended formula:

LVM (g) = 0.8{1.04[(LVIDd + PW + IVSd)3 - (LVIDd)3]} + 0.6 g.10

LVM was standardized by body surface area (BSA) and body height as LVM/BSA and LVM/height respectively.

LVH was diagnosed as LVM/BSA > 95 g/m2 in females and > 115 g/m2 in males and LVM/ height > 51 g/m2 in males and > 47 g/m2 in females according to the EACVI and ASE recommendations.12

All the information such as age, gender, height, weight, BMI, SBP, DBP, origin, smoking status, LVH on ECG criteria, LVH on echocardiography was noted in a predesigned proforma.

## DATA ANALYSIS PROCEDURE

The collected data was entered using data validation tool (MS-Excel worksheet 2010). Statistical analyses were performed with statistical software (IBM SPSS®statistics 25 for Windows). The data was presented in tables and diagrams. All measured values were reported as means ±SD for continuous variables like age, height, weight, BMI, SBP, DBP and BSA. Frequency and percentages for categorical variables like gender, area of origin, smoking status.

Sensitivity, specificity, PPV NPV and diagnostic accuracy of ECG different criteria like Sokolow-Lyon, Cornell criteria, Cornell voltage duration measurement, Romhis-Estes point scoring system for LVH was computed and echocardiography was taken as gold standard.

Receiver operating characteristic (ROC) curves and the areas under the curves analyses were conducted to compare diagnostic accuracy for the four ECG criteria using conventional cut-off values. Stata-14 software was used for ROC comparison and P<0.05 was considered of statistical significance.

## RESULTS

A total of 252 patients diagnosed with hypertension or under anti- hypertensive medications irrespective of the presenting complain were included in this study. The average age of the patients was 50.32±6.95 years. There were 157(62.3%) male and 95(37.7%) female participants The mean systolic and diastolic blood pressure was 139.92 ± 26.97 and 88.37 ± 9.61 respectively. Almost 52% patients were from urban and 48% from rural areas (figure 5). Out of 252, 50%(126) of the population were nonsmokers; 28.2% were currently smoking and 21.8% had previously smoked. Almost 78% were currently taking anti hypertensive medications. The baseline characteristics of the patients are reported in Table 1.

Out of 252 study cases, 122(48.4%) of them had left ventricular hypertrophy on Echocardiography. According to ECG criteria, left ventricular hypertrophy was observed as defined by Sokolow-Lyon criteria on 76(30.2%), as Cornell voltage criteria on 115(45.6%), as Cornell voltage duration measurement on 90(35.7%) and as Romhilt- Estes point score system on 60(23.8%) as shown in table 2.

Sensitivity, specificity, PPV, NPV and accuracy of Sokolow-Lyon criteria in diagnosis of left ventricular hypertrophy was 41.8%, 80.8%, 67.1%, 59.7% and 61.9% respectively. Likewise, diagnostics parameter of ECG by Cornell Voltage to detect LVH was 5.6%, 73.1%, 69.6% 69.3% and 69.4% respectively. Similar diagnostics parameter of ECG as defined by Cornell voltage duration measurement was 57.4%, 84.6%, 77.8%, 67.9% and 71.4% respectively and diagnostic parameters of ECG by Romhilt- Estes point score system was 36.9%, 88.5%, 75%, 59.9% and 63.5% respectively as shown in table 3. The different ECG criteria also seemed to have a better diagnostic accuracy in patients younger than 50 years of age as shown in supplementary table 1.

Receiver operating characteristic (ROC) curve for four criteria of Echocardiography to detect LVH is represented in figure 1. Area under the curve(AUC) of Sokolow-Lyon index, Cornell voltage criteria, Cornell voltage duration measurement and Romhilt-Estes point (score system was 0.613, 0.693, 0.71 and 0.627 respectively. Comparison of AUC among the ECG criteria is shown in table 4. AUC of Cornell voltage criteria and Cornell voltage duration measurement was significantly high in all criteria (p=0.038, p=0.047 and p=0.004). Our study also showed that the combined analysis of the 4 ECG criteria may have a higher diagnostic value than each ECG criterion alone as shown in supplementary table 2.

Table 1: Baseline characteristics of the patients Total: 252

| | |
|---|---|
| Males | 157 (62.3%) |
| Age (years) | 50.32 ± 6.95 |
| BMI(kg/m2) | 25.26 ± 2.66 |
| BSA(m2) | 1.77 ± 0.12 |
| SBP (mmHg) | 139.92 ± 26.97 |
| DBP (mmHg) | 88.37 ± 9.61 |
| Current use of anti-hypertensive medications(%) | 77.78 % |
| Urban residence(%) | 51.98 % |
| Smoking status<br>Current<br>Ex-smoker<br>None | <br>28.2%<br>21.8%<br>50% |

Table 2: Frequency of patients with left ventricular hypertrophy detected by electrocardiography And echocardiography

| Diagnostic criteria | LVH Positive | LVH Negative |
|---|---|---|
| Sokolow-Lyon index | 76(30.2%) | 176(69.8%) |
| Cornell voltage criteria | 115(45.6%) | 137(54.4%) |
| Cornell voltage duration measurement | 90(35.7%) | 162(64.3%) |
| Romhilt-Estes point score system | 60(23.8%) | 192(76.2%) |
| Echocardiography | 122(48.4%) | 130(51.6%) |

Table 3: Four different ecg criterias of left ventricular hypertrophy in terms of diagnostic accuracy taking echocardiographically as reference standard

| Diagnostic Criteria of ECG | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|
| Sokolow-Lyon index | 41.8% | 80.8% | 67.1% | 59.7% | 61.9% |
| Cornell voltage criteria | 65.6% | 73.1% | 69.6% | 69.3% | 69.4% |
| Cornell voltage duration measurement | 57.4% | 84.6% | 77.8% | 67.9% | 71.4% |
| Romhilt-Estes point score system | 36.9% | 88.5% | 75% | 59.9% | 63.5 |

Table 4: Pair wise comparison of four electrocardiography finding taking echocardiographically as reference standard

| ECG diagnostic criteria for LVH | | AUC | P-Value |
|---|---|---|---|
| Sokolow-Lyon index vs. | Cornell voltage criteria | 0.613 vs. 0.693 | 0.038* |
| | Cornell voltage duration measurement | 0.613 vs. 0.71 | 0.011* |
| | Romhilt-Estes point score system | 0.613 vs. 0.627 | 0.706 |
| Cornell voltage criteria vs. | Cornell voltage duration measurement | 0.693 vs. 0.71 | 0.456 |
| | Romhilt-Estes point score system | 0.693 vs. 0.627 | 0.047* |
| Cornell voltage duration measurement vs. | Romhilt-Estes point score system | 0.71 vs. 0.627 | 0.004* |

*This comparison was done by Stata-14 software*

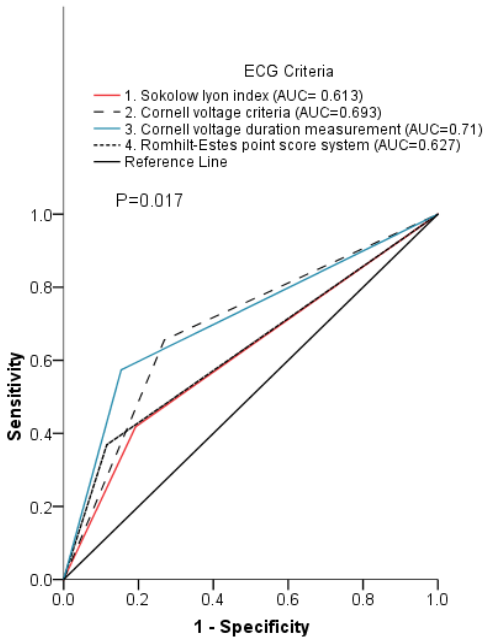


*Figure 1: receiver operating characteristic (roc) curves for four different ecg criteria in prediction of lvh*

## DISCUSSION

LVH is mainly determined by an increase in left ventricular mass, which can be estimated by the electrical voltage changes detected on the surface electrocardiogram. Because of this, the ECG is a good proxy for detecting changes in left ventricular mass. However, the electrical voltage of the heart is not only determined by the amount of myocardium present. It is instead reliant on active and passive electrical connections between the heart and torsum. These are influenced by variables such as the distance between the left ventricular cavity and the electrode, the position of the surface electrode, individual anthropometric variations, conduction problems, myocardial fibrosis, and pulmonary pathology.[13] Furthermore, the ECG voltage has been shown to vary dramatically from day to day, between patients, and even between individuals.

The only way to clarify whether or not ECG criteria are reliable in diagnosing LVH is to test them against echocardiography. In view of this, the present study evaluated the four more commonly used electrocardiographic criteria's for left ventricular hypertrophy, using echocardiography as diagnostic standard.

Our data confirms the high incidence of electrocardiographically-defined LV hypertrophy, 30.2% had LV hypertrophy as defined by Sokolow-Lyon criteria, Cornell voltage criteria 45.6%, Cornell voltage duration measurement 35.7% and Romhilt-Estes point score system 23.8%.

Certain groups of the population have showed even a higher prevalence of ECG defined Sokolow-Lyon criteria for left ventricular hypertrophy. In a study done by Sharma et al. the Sokolow-Lyon criteria was positive among 45% of 1000 young atheletes.[14]. Our study also showed similar findings that the ECG criteria seemed to have a better diagnostic accuracy in patients younger than 50 years of age.

Few previous studies investigated the accuracy of ECG criteria in the detection of LVH in Asians.[15-17] In 546 Chinese patients with hypertension, Xie et al. found that the Cornell voltage and product criteria had a higher sensitivity to detect echocardiographic LVH (28% and 36.6%, respectively).[15]

In our study Cornell Voltage and cornell voltage duration measurement criteria had had a higher sensitivity to detect echocardiographic LVH (65.6% and 57.4%) respectively. In a study done by Su et al. in Taiwan, among 539 young army men the Cornell voltage and cornell voltage duration product criteria had better performance for the echocardiographic LVH than the Sokolow–Lyon criteria, with a sensitivity of 22.2%, 27.8%, and 8.3%, respectively.[16] In 332 Korean patients, Park et al. demonstrated that the Cornell product criterion was superior to the Sokolow–Lyon voltage criterion in women, but the opposite was true in men.[17] It has been shown that QRS duration had a stronger association with Echo- LVH among all other single- lead components[18] which may have driven the better performances of Cornell- product- related criteria. QRS duration was reported to be an independent predictor for LVH in previous studies (Okin et al., 2002; Palmieri et al., 2007). Potential mechanisms included the longer time required to activate myocardium that was increasingly distant from specialized conduction tissue and the decreased conduction velocity in hypertrophied myocardium.

In the systematic review done by Pewnser et al the accuracy of different electrocardiographic indexes for the diagnosis of left ventricular hypertrophy had sensitivity ranging from 10.5-21% and median specificity of 89-99%.[5] In our study area under the curve of Cornell voltage criteria and Cornell voltage duration measurement was significantly high in all criteria (p=0.038, p=0.047 and p=0.004) and this is in accordance with previous studies by Salles et al[19] and by Xie et al.[15]

Previous studies often focused on the diagnostic sensitivity and specificity of single ECG criterion.[20,21] Our study found that the combined analysis of the 4 ECG criteria may have a higher diagnostic value than each ECG criterion alone. Also these criteria appear to have a higher diagnostic accuracy in those patients aged less than 50 years of age.

As the diagnostic accuracy of the Sokolow-Lyon criteria is comparably low, Cornell criteria and Cornell voltage duration measurement, should be implemented in routine clinical practice. In a resource-limited setting like ours where echocardiography facilities are not accessible in all rural settings, using ECG criteria such as Cornell voltage and Cornell voltage duration measurement can be considered to be standard investigations in the future for diagnosis of LVH based on the strength of their cost- effectiveness and availability. Also it has been reported that ECG-LVH can predict the outcome of heart failure outperforming MRI-LVH.[22] We also would recommend that the Cornell voltage duration algorithm be applied to the in-built software in ECG which would aid in decision making to physicians.

Our research must be understood in light of its limitations. Firstly, we just looked at four of the several ECG criteria's validated for diagnosis of LVH. Second, it was conducted in a single center. As a result, our study may be less representative than a larger multicenter study. Also left ventricular mass was established using echocardiography, cardiac magnetic resonance imaging is known to be more accurate. Nonetheless, the current study paved the way for future research in Nepal on the use of the current ECG crteria's for LVH and possibly the need of a better ECG LVH diagnosis criteria.

## CONCLUSION

In our study Cornell Voltage criteria and cornell voltage duration measurement had the higher sensitivity to detect echocardiographic LVH (65.6% and 57.4% respectively. All of the ECG criteria must be integrated with the clinical scenario. Isolated interpretation of LVH using a single ECG criteria has a low diagnostic value. In the evaluation of hypertensive patients for LVH, echocardiography is still the method of choice. However, in resource limited settings where echocardiography might not be readily available, ECG criteria such as cornell voltage and cornell voltage duration measurement can be used regularly as screening investigation for LVH because of its cost-effectiveness and easy availability.

## REFERENCES:

1. Mills KT, Stefanescu A & He J. The global epidemiology of hypertension. Nat Rev Nephrol.2020;16:223–37.
2. Blacher J, Levy BI, Mourad JJ. From epidemiological transition to modern cardiovascular epidemiology: hypertension in the 21st century. Lancet. 2016;388:
3. Ishikawa J, Ishikawa S, Kabutoya T, Gotoh T, Kayaba K, Schwartz JE, et al. Cornell product left ventricular hypertrophy in electrocardiogram and the risk of stroke in a general population. Hypertension. 2009;53(1):28-34.

4. Aro AL, Chugh SS. Clinical diagnosis of electrical versus anatomic left ventricular hypertrophy: prognostic and therapeutic implications. Circ ArrhythmElectrophysiol. 2016;9(4):e003629.

5. Pewsner D, Jüni P, Egger M, Battaglia M, Sundström J, & Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: Systematic review. BMJ. 2007;335(7622):711.

6. Zhou Y, & Zhang Y. A0420 Compatibility of left ventricular hypertrophy diagnosed by electrocardiography and by echocardiography. J Hypertension. 2018; 36.

7. Cuspidi C, Sala C, Negri F, Mancia G, Morganti A. Italian Society of Hypertension. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. J Hum Hypertens. 2012;26(6):343-349.

8. Wang D, Xu JZ, Zhang W, Chen Y, Li J, An Y, Bian R, Wang JG. Performance of Electrocardiographic Criteria for Echocardiographically Diagnosed Left Ventricular Hypertrophy in Chinese Hypertensive Patients. Am J Hypertens. 2020 Sep 10;33(9):831-836. doi: 10.1093/ajh/hpaa083. PMID: 32484222; PMCID: PMC7486900.

9. Spencer CG, Beevers DG, Lip GY. Ethnic differences in left ventricular size and the prevalence of left ventricular hypertrophy among hypertensive patients vary with electrocardiographic criteria. J Hum Hypertens 2004; 18:631–636.

10. Unger T, Borghi C, Charchar F. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens 2020; 38:982-85.

11. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M. et al. Recommendations on the Use of Echocardiography in Adult Hypertension: A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J American Society of Echocardiography. 2015;28(7), 727-754.

12. International Obesity Task Force. The Asia-Pacific perspective : redefining obesity and its treatment. World Health Organization – WesternPacificRegion.2000

13. Peguero J, Lo Presti S, Perez J, et al. Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy. J Am Coll Cardiol. 2017 Apr, 69 (13) 1694–1703.

14. Sharma S, Whyte G, Elliott P, Padula M, Kaushal R, Mahon N, et al. Electrocardiographic changes in 1000 highly trained junior elite athletes. Br J Sports Med 1999;33:319-324.

15. Xie L, Wang Z. Correlation between echocardiographic left ventricular mass index and electrocardiographic variables used in left ventricular hypertrophy criteria in Chinese hypertensive patients. Hellenic J Cardiol 2010; 51:391–401.

16. Su FY, Li YH, Lin YP, Lee CJ, Wang CH, Meng FC, et al. A comparison of Cornell and Sokolow-Lyon electrocardiographic criteria for left ventricular hypertrophy in a military male population in Taiwan: the cardiorespiratory fitness and hospitalization events in armed forces study. Cardiovasc Diagn Ther 2017; 7:244–251.

17. Park JK, Shin JH, Kim SH, Lim YH, Kim KS, Kim SG, et al. A comparison of Cornell and Sokolow-Lyon electrocardiographic criteria for left ventricular hypertrophy in Korean patients. Korean Circ J 2012; 42:606–613.

18. Lv, T., Yuan, Y., Yang, J., Wang, G., Kong, L., Li, H., Li, X., Sun, Y., Li, X., Zhang, Z., Cheng, X., Wu, L., Tan, X., Han, B., Li, H., Zhang, Z., Wang, J., Wu, Y., Wang, Y., Guo, J., ... Zhang, P. (2021). The association between ECG criteria and Echo criteria for left ventricular hypertrophy in a general Chinese population. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc, 26(5), e12880.

19. Salles G, Leocádio S, Bloch K, Nogueira AR, Muxfeldt E. Combined QT interval and voltage criteria improve left ventricular hypertrophy detection in resistant hypertension. Hypertension. 2005;46(5):1207–12.

20. Jaggy C, Perret F, Bovet P, van Melle G, Zerkiebel N, Madeleine G, et al. Performance of classic electrocardiographic criteria for left ventricular hypertrophy in an African population. Hypertension 2000; 36:54–61.

21. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage duration products. J Am Coll Cardiol 1995; 25:417–23.

22. Oseni, A. O., Qureshi, W. T., Almahmoud, M. F. et al (2017). Left ventricular hypertrophy by ECG versus cardiac MRI as a predictor for heart failure. Heart, 103(1), 49–54.

Case Report

Nepalese Heart Journal 2024; Vol 21(1), 49-50

# Undiagnosed Hypothyroidism: Culprit for Fenofibrate Induced Rhabdomyolysis

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## Abstract

Fenofibrate induced rhabdomyolysis is not very common event. We present a case of muscle pain and generalized weakness following administration of fenofibrate for 10 days in undiagnosed hypothyroidism. Patient gradually improved after stopping the drug. As per our knowledge, this is probably the first case report of fenofibrate induced rhabdomyolysis from Nepal.

**Keyword:** Fenofibrate, hypothyroidism, rhabdomyolysis.

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## Introduction

Hypothyroidism on many occasions may remain undiagnosed as symptoms of hypothyroidism are vague. There are many clinical situations in which patients are taking different medicines in the case of undiagnosed hypothyroidism.

Fibric acid derivatives such as fenofibrate increases high density lipoprotein (HDL) and lowers low density lipoprotein (LDL), total plasma cholesterol, very low-density lipoprotein (VLDL) and triglyceride. Fenofibrate has half-life of about 20 hours, is 99% protein-bound with 80% excretion via urine. One of the most serious side-effect is rhabdomyolysis and myopathy.[1]

Myopathy in hypothyroidism generally present as elevation of serum creatinine phosphokinase (CPK), muscle pain and stiffness, proximal muscle weakness and cramps.[2,3] Rhabdomyolysis is a syndrome involving skeletal muscle necrosis and the consequent release of intracellular muscle proteins and electrolytes into the systemic circulation. Its severity is variable, ranging from asymptomatic elevations in serum muscle enzymes levels to life-threatening electrolyte disturbances and acute renal failure.[4] The typical clinical presentation includes muscle weakness, myalgias and dark-colored urine due to myoglobinuria, and the diagnosis is usually established by elevated serum skeletal muscle enzyme levels.[5] Creatinine phosphokinase is the most sensitive indicator of muscle injury and, although there is no defined serum cut-off level for the diagnosis, many clinicians use five to ten times the upper limit of normal range.[6] Only few articles have been reported on fenofibrate induced rhabdomyolysis in patients of hypothyroidism in other settings.[1,7] No case have been reported in the settings similar to ours as per our best knowledge. We report a case of 38 years male of undiagnosed hypothyroidism culprit for fenofibrate induces rhabdomyolysis.

## Case report:

A 38 years male, non-smoker, non-alcohol consumer, known case of systemic hypertension under medication, recently diagnosed as hypertriglyceridemia (triglyceride [TG] level of 6.5 mmol/L) and started on fenofibrate 160 mg since last 10 days came with complain of generalized weakness and bilateral pain in arms, thighs and buttocks since last 10 days. He denied any history suggestive of inherited muscle disease. He complained of undue fatigue and difficulty in mobilization. The patient was having inadequate urine output since same duration however there was no history of swelling of limbs. On examination, patient had generalized muscle tenderness and proximal muscle weakness.

The diagnosis of rhabdomyolysis in this patient was established on the basis of myalgia, muscle weakness, prominent elevation of serum levels of CPK, lactate dehydrogenase, aspartate aminotransferase and also creatinine. The fenofibrate was discontinued, thyroid hormone replacement was started with oral levothyroxine (50mcg/day) and intravenous fluid replacement with normal saline was started. The urine output was normalized, and serum urea and creatinine decreased to normal values during hospital stay. The patient's maximal weakness was observed on the seventh day following the onset of weakness. The patient started improving on the tenth day following stoppage of the offending drug.

Investigations at admission, discharge and follow up are shown in Table 1.

**Table 1:** Serial investigations of the patient from admission till follow up.

| | At admission | After 1 week | After 1 month | After 3 months |
|---|---|---|---|---|
| CPK-TOTAL | 39463 IU/L | 29021 IU/L | 474 IU/L | 234 IU/L |
| CREATININE | 1.3 mg/dL | 1.2 mg/dL | 0.9mg/dL | 0.9mg/dL |
| POTASSIUM | 4.0 MEQ/L | 3.9 MEQ/L | 5.1 MEQ/L | 4.8 MEQ/L |
| ALT | 501 IU/L | 470 IU/L | 24 IU/L | 71 IU/L |
| AST | 2076 IU/L | 859 IU/L | 20 IU/L | 36 IU/L |
| TG | 2.2 MMOL/L | | | 3.3 MMOL/L |
| LDL | 2.2 MMOL/L | | | 1.6 MMOL/L |
| TOTAL CHOLESTEROL | 4.3 MMOL/L | | | 3.1 MMOL/L |
| URINE MYOGLOBIN | >12000 MICROGRAM/L | | | |
| TSH | 137 uIU/ML | | 70.2 uIU/ML | 2.87 uIU/ML |

## Discussion:

Hypothyroidism is an established secondary cause of dyslipidemia, but it is also a potential risk factor of myopathy induced by lipid-lowering agents.[8-11] Fenofibrate monotherapy-induced rhabdomyolysis is very rare event. Thus, other risk factor like hypothyroidism should be suspected, in cases of fenofibrate induced rhabdomyolysis.[12] Once diagnosed, it is mandatory to stop fibrates and start IV hydration along with correction of hypothyroidism. Our patient started recovering after 2 days and his myopathy improved after 10 days. In cases of rhabdomyolysis, rechallenge of the treatment is not advised because of the risk of a serious relapse. Treatment of hypothyroidism itself should lower the TG level in these cases.[13] Isolated hypothyroidism leading to rhabdomyolysis is a rare and literatures have recommended to search for other precipating factors like statin therapy and heavy exercise.[14] Our patient recovered completely after stopping fenofibrate and subsequently adding oral levothyroxine.

The study has few limitations. The demarcation of cause of improvement on the patient could have been contributed by both of the measures of adding levothyroxine and stopping fenofibrate. We didn't consider muscle biopsy and genetic testing in the patient as the patient recovered almost completely in follow up.

## Conclusion:

Hypothyroidism increase the chance of myopathy and should be checked in all patients of dyslipidemia who are planned to be treated with fenofibrate.

## References:


1. Ghosh B, Sengupta S, Bhattacharjee B, Majumder A, Sarkar S B. Fenofibrate-induced myopathy. Neurol India 2004;52:268-9
2. Sekine N, Yamamoto M, Michikawa M, Enomoto T, Hayashi M, Ozawa E, et al. Rhabdomyolysis and acute renal failure in a patient with hypothyrodism. Int Med. 1993;32(3):269-71.
3. Soltani P, Rezvanfar MR, Pirasteh S. Acute renal failure in a patient with Sheehan Syndrome and rhabdomyolysis. IJKD. 2008;2(1):50-2.
4. Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis--an overview for clinicians. Crit Care. 2005;9(2):158-69.
5. Sauret J, Marinides G, Wang G. Rhabdomyolysis. Am Fam Phys. 2002;65(5):907-12.
6. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Intern Emerg Med. 2007;2(3):210-8.
7. Wang D, Wang Y. Fenofibrate monotherapy-induced rhabdomyolysis in a patient with hypothyroidism: A rare case report and literature review. Medicine. 2018 Apr;97(14).
8. Al-Jubouri MA, Briston PG, Sinclair D, Chinn RH, Young RM. Les- son of the week: myxoedema revealed by simvastatin induced myopathy. BMJ. 1994;308(6928):588.
9. Tokinaga K, Oeda T, Suzuki Y, Matsushima Y. HMG-CoAreducta- se inhibitors (statins) might cause high elevations of creatinine phosphokinase (CK) in patients with unnoticed hypothyroidism. Endocr J. 2006;53(3):401-5.
10. OlukogaAO, CrowleyVEF, LawalA, Weinkove C. Hyperlipidaemia and hypothyroidism. Screen patients for hypothyroidism before treatment. BMJ. 1994;308(6933):918.
11. Kisch E, Segall HS. Interaction between simvastatin and L-thyro- xin. Ann Int Med. 2005;143(7):547.
12. Tahmaz M, Kumbasar B, Ergen K, Ure U, Karatemiz G, Kazancio- glu R. Acute renal failure secondary to fenofibrato monotherapy- induced rhabdomyolysis. Ren Fail. 2007;29(8):927-30.
13. Le Quintrec JS, Le Quintrec JL. Drug-induced myopathies. Baillieres Clin Rheumatol 1991;5:21-38.
14. Gurala D, Rajdev K, Acharya R, Idiculla PS, Habib S, Krzyzak M. Rhabdomyolysis in a young patient due to hypothyroidism without any precipitating factor. Case Reports in Endocrinology. 2019 Dec 3;2019.

Case Report

Nepalese Heart Journal 2024; Vol 21(1), 51-54

# Acute Coronary Syndrome in a Patient with Sarcoidosis: A Case Report

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## Abstract

Sarcoidosis is a complex systemic disorder characterized by an increased cellular immune response and the development of non-caseating granulomas. Sarcoidosis can affect any other organ and cardiac involvement has been reported in a substantial percentage of individuals. A sound clinical evaluation is needed for rapid recognition and implementation of appropriate treatment alternatives. Chest pain is a common presenting symptom in sarcoidosis. We present here an interesting case of a 39-year-old female presenting with ST elevation myocardial infarction who was managed by primary percutaneous intervention.

**Key words:** Acute coronary syndrome, Coronary Angiography, Coronary Intervention, Sarcoidosis

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## Introduction

Sarcoidosis is a complex systemic disorder characterized by an increased cellular immune response and the development of non-caseating granulomas. Because it can affect practically every organ in the body, it can induce a wide range of clinical symptoms.[1] The etiology of sarcoidosis is unknown, and because it can mimic other common clinical illnesses, diagnosing it can be difficult. Although the prognosis can be improved, early discovery and vigorous treatment are required.[1]

While sarcoidosis can affect many other organs, cardiac involvement has been reported in a substantial percentage of individuals. The first recorded case of cardiac sarcoidosis occurred in1929, and subsequent autopsy studies have showed that up to 76% of sarcoidosis patients have cardiac involvement.[2] Despite its prevalence, cardiac sarcoidosis is commonly misdiagnosed because it resembles other heart illnesses. A sound clinical evaluation is needed for rapid recognition and implementation of appropriate treatment alternatives.[3]

Studies suggest that sarcoidosis results from the combination of immune dysregulation, environmental factors, and genetic predisposition.[6]

Sarcoidosis can present clinically in a variety of ways depending on the organs involved. Typical symptoms include fatigue, weight loss, fever, and general malaise. Pulmonary involvement is the most common sarcoidosis symptom, and patients usually complain of chest pain, shortness of breath, and coughing. Sarcoidosis, on the other hand, can affect the skin, eyes, liver, spleen, lymph nodes, and neurological system causing a variety of symptoms and issues.[7]

Chest pain is a common presenting symptom in sarcoidosis. Perfusion defects indicative of myocardial ischemia was detected in almost 50% cases in a study focusing on the importance of angina in sarcoidosis patients.[4] It is important to note that, despite the discovery of myocardial involvement, epicardial coronary involvement was not pathologically established in explanted hearts untilrecently.[5]

Sarcoidosis must be diagnosed using clinical evaluation, imaging studies, laboratory tests, and histological analysis. The first evaluation includes a detailed medical history and physical examination to search for any possible organ involvement symptoms. Laboratory tests may reveal abnormalities such as hypercalcemia, liver dysfunction, or elevated angiotensin-converting enzyme (ACE) levels. These findings, however, can be discovered in a variety of disorders, not just sarcoidosis.

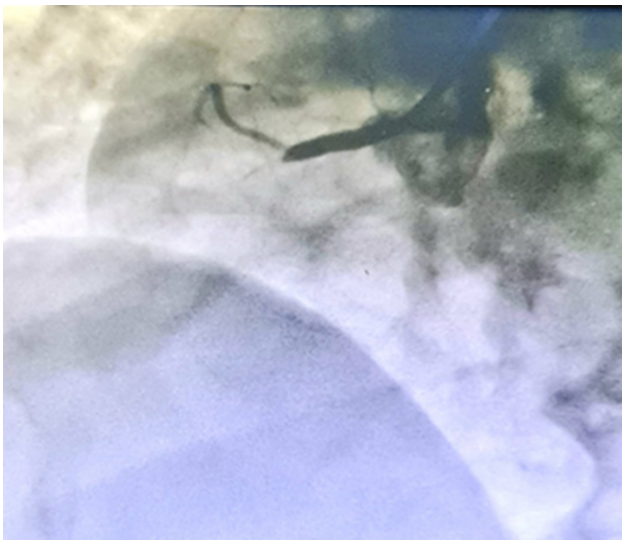

*Figure 1: Coronary angiogram showing total occlusion in Proximal RCA.*

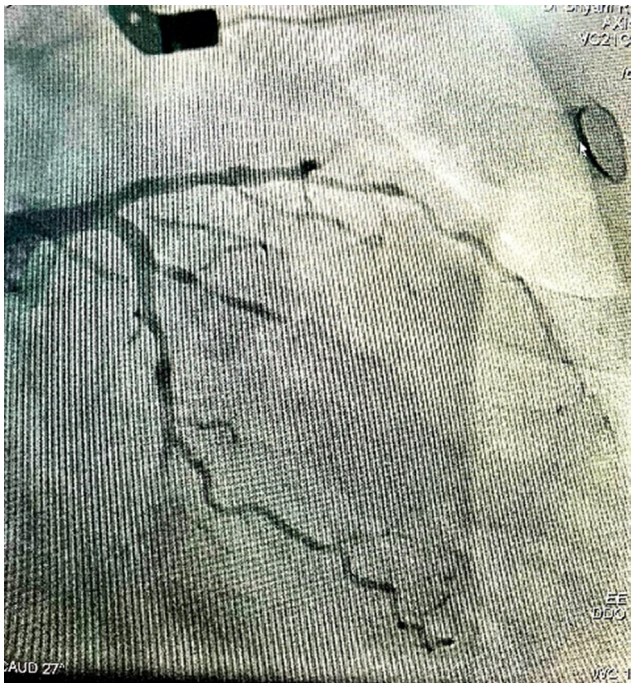

*Figure 2: Coronary angiogram showing 100% stenosis in mid LAD and diffused disease in LCX and OMI*

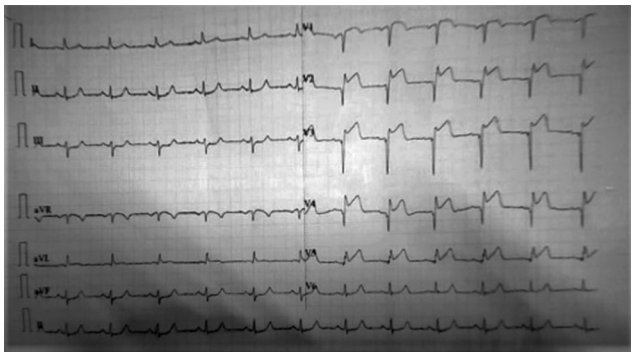

*Figure 3: ECG revealed ST elevation in V1-V4 with reciprocal ST depression in II, III and aVF.*

Imaging investigations, such as chest X- rays, CT scans, or magnetic resonance imaging (MRI), are critical for establishing organ involvement and assessing disease severity. Sarcoidosis is distinguished by pulmonary infiltrates and bilateral hilar lymphadenopathy. Other imaging modalities, including as positron emission tomography (PET) scans, can help determine extra pulmonary involvement and disease activity.

For a definitive diagnosis of sarcoidosis, histopathological evidence of non-caseating granulomas is required. A biopsy of the affected organ or tissue is typically performed to do this. A heart biopsy in patients with cardiac sarcoidosis may be difficult to acquire because to its invasive nature. However, in some cases where there is a high clinical suspicion, cardiac samples or even explanted heart testing may be required to establish the diagnosis.[9]

When a diagnosis of sarcoidosis is made, the severity and amount of organ involvement decide how the disease should be managed. Sarcoidosis may occasionally resolve on its own or require only supportive care. However, when organ function is severely damaged or the disease is progressing, medication is essential to control inflammation and avert the consequences.[10]

## Case Presentation

A 39-year-old woman, presented with chest pain, and shortness of breath that had been persistent for five days. She was a known case of Sarcoidosis for five years. She was diagnosed to have hypertension and type2diabetes for two years. She was treated for pulmonary tuberculosis on clinical grounds. No improvement in symptoms even after completion of anti-tubercular therapy warranted further evaluation.

During work up her angiotensin-converting enzyme (ACE) level was elevated the value was more than 300 U/L; normal value 12-68 U/L. On USG abdomen and pelvis, she had hepatomegaly and numerous intraabdominal lymph nodes. A true cut biopsy of the liver was done and reported as many lymphoid and fibrous tissue-encircled non-caseating epithelioid cell granulomas. The findings of Granulomatous inflammation on liver biopsy pointed to liver involvement in sarcoidosis.

After diagnosis of Sarcoidosis was made, she was being treated with azathioprine 50mg and prednisolone as and when required. She was doing well one day prior to presentation at our center.

On evaluation at our center the ECG revealed ST elevation in V1-V4 with reciprocal ST depression in II, III and AVF. Her Qualitative Troponin done outside center was positive. Diagnosis of anteroseptal STEMI was made. Echocardiography revealed hypokinesia of Left anterior descending artery (LAD) territory and LVEF of 35%. Coronary angiogram was performed and diagnosis of triple vessel disease involving LAD, Right coronary artery (RCA) and Left circumflex artery (LCX) was made. PCI was performed on LAD and RCA.

Her condition was stable at the time of discharge. She was discharged on Dual antiplatelet therapy (DAPT), Sodium Glucose Transporter 2 (SGLT2) inhibitors, Mineralocorticoid receptor antagonist (MRA), Angiotensin receptor blocker (ARB), Diuretics and azathioprine. Prednisolone therapy was avoided keeping in consideration the acute myocardial infarction.

On follow-up she did not have complaints of chest pain or chest heaviness. Her vitals were stable with LVEF of 45% on 2D echo.

## Discussion:

A systemic inflammatory illness called sarcoidosis is characterized by the development of non-caseating granulomas in the organs that are afflicted. Heart failure, conduction problems, arrhythmias, and sudden cardiac death are just a few of the manifestations that can result from cardiac involvement in sarcoidosis, often known as cardiac sarcoidosis (CS). The connection between sarcoidosis and ACS is, however, not very common.[11] However, our patient had cardiac involvement in terms of heart failure and coronary artery disease which was very less commonly reported.

Uncertainty exists regarding the precise pathophysiological mechanisms behind the ACS development in sarcoidosis. The infiltration of coronary arteries by sarcoid granulomas is thought to cause luminal constriction and ensuing myocardial ischemia. The development of atherosclerosis and plaque instability may be aided by inflammation and fibrosis within the artery walls, raising the risk ofACS.[12]

It was unexpected, nonetheless, for ACS to develop alongside sarcoidosis.[13] Our diagnosis was supported with initial findings of

non-caseating granulomas in the liver biopsy and increase level of ACE. In our case indicated that the patient, had a known history of sarcoidosis.

Patient was diagnosed with diabetes and hypertension for short duration of two years. There was absence of any other traditional risk factor for coronary artery disease in this young lady. At the time of diagnosis of sarcoidosis there was involvement of liver and lungs. The nature of presentation in this case supported the causal role of disease in development of acute MI.

Due to the necessity to combine antiplatelet and anticoagulant medications with the danger of aggravating granulomatous inflammation, the management of ACS in patients with sarcoidosis can be difficult. Due to the amount and severity of coronary artery disease in our situation, revascularization was advised.[14] This strategy was designed to increase the myocardial blood flow and reduce symptoms. The treatments also included antiplatelet medications, statins, beta-blockers, and angiotensin receptor blockers.[15]

The management of her illness was made difficult by the existence of numerous comorbidities, including hypertension, type 2 diabetes, and her coronary artery disease most likely developed and progressed as a result of these comorbidities. As prolonged inflammation and the development of granulomas can have resulted in vascular dysfunction and a prothrombotic condition, sarcoidosis itself may have contributed to the emergence of ACS.[16]

In order to effectively manage patients with sarcoidosis and ACS over the long term, medical therapy must be optimized with frequent follow-up visits. Ventricular arrhythmias and sudden cardiac death are likely to occur in ACS patients, hence, implanted cardioverter-defibrillator (ICD)insertion may be considered in certain circumstances.[17]

## Conclusion:

The necessity of taking sarcoidosis into account as a possible underlying cause in patients who come with ACS is highlighted by this case, especially in those who have a history of sarcoidosis or suspicious clinical characteristics. For these patients' results to be maximized, early identification and adequate therapy are essential. Unanswered questions that whether the pathophysiology and behavior of the coronary artery disease remains different in this subset of patients' needs to be addressed. Alternative therapies which have less deleterious effect on long term basis needs to be sought. More investigation is required to comprehend the pathophysiological pathways that connect sarcoidosis and ACS and to create specialized treatment plans for this particular population.

## References


1. Sève P, Pacheco Y, Durupt F, Jamilloux Y, Gerfaud-Valentin M, Isaac S, et al. Sarcoidosis: A Clinical Overview from Symptoms to Diagnosis. Cells. 2021 Mar 31;10(4):766. doi : 10.3390/cells10040766
2. Sekhri V, Sanal S, DeLorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. Archives of Medical Science : AMS [Internet]. 2011 Aug 1 [cited 2021 Nov 4];7(4):546–54. doi: 10.5114/aoms.2011.24118
3. Nunes H, Bouvry D, Soler P, Valeyre D. Sarcoidosis. Orphanet Journal of Rare Diseases [Internet]. 2007;2(1):46. Available from: https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-2-46 doi: 10.1186/1750-1172-2-46
4. Truong, Justina, and John Ashurst. "A Case Report of Pulmonary Sarcoidosis: An Uncommon Cause of Chest Pain." Clinical Practice and Cases in Emergency Medicine, vol. 4, no. 4, 9 Sept. 2020, pp. 645–648, www.ncbi.nlm.nih.gov/pmc/articles/PMC7676790/ . doi: 10.5811/cpcem.2020.7.48310
5. Uthurralt, N, et al. "Thallium-201 Scintigraphy for Diagnosis of Old Myocardial Infarction: Comparison with Electrocardiographic, Ventriculographic, and Coronary Arteriographic Findings." Heart, vol. 43, no. 5, 1 May 1980, pp. 527–534. doi: 10.1136/hrt.43.5.527
6. Jain, Rashi, et al. "Sarcoidosis: Causes, Diagnosis, Clinical Features, and Treatments." Journal of Clinical Medicine, vol. 9, no. 4, 10 Apr. 2020, p. 1081, https://doi.org/10.3390/jcm9041081. Doi: 10.3390/jcm9041081
7. Nunes, Hilario, et al. "Sarcoidosis." Orphanet Journal of Rare Diseases, vol. 2, no. 1, 2007, p. 46, ojrd.biomedcentral.com/articles/10.1186/1750-1172-2-46, https://doi.org/10.1186/1750-1172-2-46. Doi: 10.1186/1750-1172-2-46
8. Crouser, Elliott D., et al. "Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline." American Journal of Respiratory and Critical Care Medicine, vol. 201, no. 8, 15 Apr. 2020, pp. e26–e51, https://doi.org/10.1164/rccm.202002-0251st.
9. Melani, Andrea S., et al. "A Comprehensive Review of Sarcoidosis Diagnosis and Monitoring for the Pulmonologist." Pulmonary Therapy, 6 June 2021, link.springer.com/article/10.1007%2Fs41030-021-00161-w, https://doi.org/10.1007/s41030-021-00161-w
10. Ungprasert, Patompong, et al. "Clinical Manifestations, Diagnosis, and Treatment of Sarcoidosis." Mayo Clinic Proceedings: Innovations, Quality & Outcomes, vol. 3, no. 3, Sept. 2019, pp. 358–375, https://doi.org/10.1016/j.mayocpiqo.2019.04.006.
11. Lehtonen, Jukka, et al. "Cardiac Sarcoidosis: Phenotypes, Diagnosis, Treatment, and Prognosis." European Heart Journal, vol. 44, no. 17, 16 Mar. 2023, p. ehad067, pubmed.ncbi.nlm.nih.gov/36924191/, https://doi.org/10.1093/eurheartj/ehad067.
12. Gonen, Tal, et al. "The Association between Sarcoidosis and Ischemic Heart Disease—a Healthcare Analysis of a Large Israeli Population." Journal of Clinical Medicine, vol. 10, no. 21, 29 Oct. 2021, p. 5067, www.ncbi.nlm.nih.gov/pmc/articles/PMC8584952/, https://doi.org/10.3390/jcm10215067. Accessed 8 Mar. 2023.
13. "Hepatic Sarcoidosis." Journal of Clinical and Translational Hepatology, vol. 1, no. 2, 1 Dec. 2016, https://doi.org/10.14218/jcth.2013.00016. .
14. Sopek Merkaš, Ivana. "Antiplatelet Therapy after Coronary Artery Bypass Graft Surgery – Unevenness of Daily Clinical Practice." Acta Clinica Croatica, 2021, https://doi.org/10.20471/acc.2021.60.03.26.
15. Kumar, Amit, and Christopher P Cannon. "Acute Coronary Syndromes: Diagnosis and Management, Part I." Mayo Clinic Proceedings, vol. 84, no. 10, 2009, pp. 917–38, www.ncbi.nlm.nih.gov/pmc/articles/PMC2755812/, https://doi.org/10.1016/S0025-6196(11)60509-0.

16. Leon, Benjamin M, and Thomas M Maddox. “Diabetes and Cardiovascular Disease: Epidemiology, Biological Mechanisms, Treatment Recommendations and Future Research.” World Journal of Diabetes, vol. 6, no. 13, 10 Oct. 2015, p. 1246, www.ncbi.nlm.nih.gov/pmc/articles/PMC4600176/, https://doi.org/10.4239/wjd.v6.i13.1246.

17. Skowasch, Dirk, et al. “Management of Sudden Cardiac Death in Cardiac Sarcoidosis Using the Wearable Cardioverter Defibrillator.” PLOS ONE, vol. 13, no. 3, 22 Mar. 2018, p. e0194496, https://doi.org/10.1371/journal.pone.0194496.

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