Original Article

# Effect of Carica papaya Leaf Extract in Cyclophosphamide -induced Thrombocytopenic Long Evan's Male Rats

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## Abstract

**Background:** Thrombocytopenia, particularly due to dengue and other causes, is a significant health concern in our country, often leading to various hematological abnormalities. Historically, Carica papaya leaf has been employed in various ethnomedicinal systems in different asian and pacific countries for mitigating such abnormalities.

**Objective:** This study hence aims to evaluate the effect of C. papaya leaf extract on platelet count in cyclophosphamide-induced thrombocytopenic Long Evans male rats.

**Methods:** Thirty healthy male Long Evans rats, aged 8-10 weeks and weighing 150-250 grams, were used. After a 14-day acclimatization period, the rats were divided into two groups: a control group (Group A) and an experimental group (Group B). Group A was further subdivided into a baseline control (A1) and a cyclophosphamide-induced thrombocytopenic control (A2). Both Group A2 and Group B received cyclophosphamide (70 mg/kg/day) on days 1, 3, and 5 to induce stable thrombocytopenia, along with a basal diet. Group B also received C. papaya leaf extract (400 mg/kg) orally from days 10 to 23. Blood samples were collected on days 1, 10, and 24 for platelet, RBC, and WBC counts, as well as biochemical analysis. Statistical analysis was performed using SPSS software (version 22).

**Results:** By day 10, both Group A2 and Group B showed a significant decrease in mean platelet count ($p<0.001$) and significant increases in bleeding time (BT) and clotting time (CT) ($p<0.001$) compared to day 1 and Group A1. By day 24, Group A2 continued to exhibit a significant decrease in platelet count ($p<0.001$) and increases in BT and CT ($p<0.001$) compared to day 1, Group A1, and Group B. Conversely, Group B showed a significant increase in platelet count ($p<0.001$) and reductions in BT and CT ($p<0.001$) compared to day 10 and Group A2. Additionally, RBC and WBC counts were significantly lower in Group A2 on day 24, while Group B showed significantly higher RBC and WBC counts compared to Group A2, with levels nearly matching those of Group A1.

**Conclusion:** C. papaya leaf extract could effectively increase platelet, RBC, and WBC counts in cyclophosphamide-induced thrombocytopenic rats, demonstrating its potential for managing thrombocytopenia.

**Keywords:** Thrombocytopenia, Cyclophosphamide, Carica papaya leaf, Long Evans male rats.

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## Introduction

Thrombocytopenia, defined as a significantly reduced platelet count, typically does not cause bleeding until levels drop below 50,000/µl, compared to the normal range of 150,000 to 300,000/µl[1]. The primary causes include impaired platelet production in conditions like bone marrow failure, megaloblastic anemia, and leukemia, or increased platelet destruction due to disorders such as idiopathic thrombocytopenic purpura, SLE, viral infections like dengue and chikungunya, and drug-induced thrombocytopenic purpura[2]. Thrombocytopenia is a common and

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dangerous symptom of dengue fever, often leading to severe complications such as Dengue Hemorrhagic Fever and Dengue Shock Syndrome[3,4]. With nearly half of the world's population at risk, dengue has seen a dramatic rise, now affecting an estimated 100-400 million people annually. Severe cases are a major cause of illness and death in parts of Asia and Latin America. Despite no specific treatment, early detection and proper care can reduce fatality rates to below 1%[5].

Despite extensive research, effective treatments for dengue are still in the early stages. Several antiviral agents and immune modulators are under clinical evaluation but won't be available for clinical use soon[6]. While some dengue vaccines are in development and a few have been licensed, they lack convincing efficacy across all age groups and do not provide immunity against all serotypes[7]. The absence of effective dengue treatments has sparked interest in alternative therapies, such as Carica papaya Linn (Caricaceae) leaf juice, traditionally used in Sri Lanka, Malaysia, and parts of India to boost platelet counts in dengue patients[8]. Recent research highlights the medicinal potential of papaya, now recognized as a valuable nutraceutical plant. Phytochemical analysis of C. papaya leaves has identified the presence of bioactive compounds, including flavonoids, saponins, and alkaloids, which offer significant medicinal benefits[9].

C. papaya (CP) leaf extract is believed to have antiviral and hematological benefits that may aid in treating dengue. It significantly inhibits hemolysis and may help stabilize biological membranes[10]. The extract also exhibits notable antioxidant and free radical scavenging properties, making it valuable for pharmaceutical and nutritional uses[11]. Additionally, the leaf's high alkaloid content, alongside cardiac glycosides and polyphenols, shows no adverse effects on liver enzymes, suggesting it is non-toxic to the liver[12]. Phytochemical analysis further reveals the presence of tannins and flavonoids, indicating potential nephroprotective and antioxidant effects, useful in treating renal disorders[13].

As C. papaya leaf consumption increasingly gains attention for therapeutic uses, it is important to evaluate the in vivo potential. Henceforth, the present study aims to evaluate the effect of C. papaya leaf extraction.

**Methodology**

Study Settings and Population: This study was designed as experimental animal study. This study was conducted in the Department of Physiology at Sir Salimullah Medical College, Dhaka, Bangladesh. The study period was January 2021 to December 2021 for a period of one year. Apparently, healthy long Evans male rats, 8-10 weeks of age, weighing 150-250 g were collected from the Animal Resource Facility, International Center for Diarrheal Disease Research, (ICDDRB), Dhaka, Bangladesh. Unhealthy or diseased rats were excluded from this study.

Grouping of the Rats: After a 14-day acclimatization period, 30 male Long Evans rats were randomly divided into two main groups. Group A (control) was further split into Group A1 (10 rats) receiving a basal diet for 23 days, and Group A2 (10 rats) receiving a basal diet plus subcutaneous cyclophosphamide (70 mg/kg) on days 1, 3, and 5. Group B (experimental) consisted of 10 rats, also receiving a basal diet and cyclophosphamide (70 mg/kg) on the same days, followed by oral administration of C. papaya leaf aqueous extract (400 mg/kg/day) from days 10 to 23.

Intervention: Group A1, consisting of 10 rats, served as the baseline control, receiving only a basal diet for 23 days. Group A2, also comprising 10 rats, acted as the cyclophosphamide-induced thrombocytopenic control group; in addition to the basal diet, these rats received subcutaneous injections of cyclophosphamide (70 mg/kg body weight) on days 1, 3, and 5. Group B, the experimental group, consisted of 10 thrombocytopenic rats treated with C. papaya leaf aqueous extract. These rats received the same cyclophosphamide injections as Group A2, followed by oral administration of C. papaya leaf extract (400 mg/kg body weight) via gastric gavage daily from day 10 to day 23. All treatments were administered between 09:00 AM and 10:00 AM for twenty-three consecutive days (from Day 1 to day 23).

Study Procedure: All rats were housed in the Animal Facility of the Institution of Nutrition and Food Science at Dhaka University, where the experiment was conducted. Prior to the intervention, the rats underwent a 14-day acclimatization period under standard laboratory conditions (temperature: 27-28°C; 12-hour light/dark cycle). During the acclimatization period, the rats had ad libitum

access to food and water. Following acclimatization, the experiment was conducted over a 23-day period. Body weight measurements were recorded at the start of the study (Day 1) and again at the end (Day 23).

On day 1, baseline measurements of platelet count, bleeding time, and clotting time were taken for all rats. Thrombocytopenia was induced in Group A2 (Cyclophosphamide-induced thrombocytopenic control) and Group B (Experimental) via subcutaneous injections of cyclophosphamide (70 mg/kg) on days 1, 3, and 5. Group A1 (Baseline control) received a regular diet. The rats were then observed for 4 days to allow stable thrombocytopenia to develop.

On day 10, platelet count, bleeding time, and clotting time were reassessed. As expected, Group A1 maintained normal values, while Groups A2 and B exhibited thrombocytopenia, with prolonged bleeding and clotting times due to cyclophosphamide administration.

Starting on day 10, Group B was treated with C. papaya aqueous leaf extract (400 mg/kg body weight) via oral gavage daily for 14 days, administered between 09:00 and 10:00 AM. Group A2 continued on a basal diet throughout the treatment period.

Again, blood was withdrawn on day-10 and platelet count, BT and CT were estimated. On day 24, all the rats were anaesthetized with the aid of chloroform (30%) and were sacrificed. After sacrificing the rats, platelet, RBC and WBC count were estimated by Sysmex XE-5000 Automated Hematology Analyzer at the Department of Pathology, Bangabandhu Sheikh Mujib Medical University (BSMMU). Bleeding Time was done by Duke's method and Clotting Time was done by capillary method.

Statistical Analysis: Statistical analysis was done by using Statistical Package of Social Science (SPSS) windows version 22. Data were presented as mean ± SD. One way ANOVA test was performed for comparison among the groups and then post hoc-Bonferroni test was done to compare between groups. Paired t test and Fisher's Exact test were done as applicable. A p-value of ≤0.05 was considered the threshold for statistical significance.

Ethical Approval: Protocol was approved by the Institutional Ethics Committee (IEC) of Sir Salimullah Medical College (SSMC), Dhaka, Bangladesh.

**Results**

The mean ± SD platelet count on day-1 were 575.40 ± 82.37, 526.50 ± 99.00 and 599.00 ± 140.67 K/µl; on day-10 were 561.00 ± 78.80, 115.50 ± 8.96 and 113.50 ± 14.15 K/µl; and on day-24 were 563.00 ± 79.17, 159.00 ± 27.26 and 574.00 ± 107.52 K/µl in group A1, group A2 and group B, respectively (Figure:1).

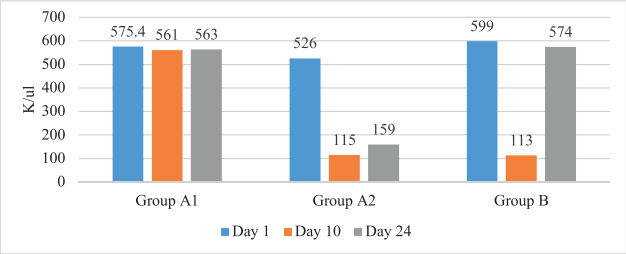



**Figure 1:** Comparison of mean Platelet count in different groups of rats (N=30)

The mean ± SD platelet count on day 1 was similar across all groups, with no statistically significant differences. By day 10, the platelet count was significantly lower ($p<0.001$) in groups A2 and B compared to group A1, but the difference between groups A2 and B was not significant. On day 24, group A2 had a significantly lower platelet count ($p<0.001$) compared to both groups A1 and B, while the counts in groups A1 and B were similar with no significant difference. In group A1, the mean platelet count remained consistent across days 1, 10, and 24, with no significant changes. In contrast, group A2 showed a significant decrease ($p<0.001$) in platelet count on days 10 and 24 compared to day 1. Group B also exhibited a significant decrease ($p<0.001$) on day 10 compared to day 1, followed by a recovery on day 24, where the platelet count was similar to day 1, with no significant difference (Table I and II).

**Table I:** Multiple comparison of mean platelet count at day-1, day-10 & day-24 within different groups of rats (N=30)

| Group | p-value | | |
|---|---|---|---|
| | Group A1 | Group A2 | Group B |
| Day 1 vs Day 10 | 0.429 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| Day 1 vs Day 24 | 0.620 $^{ns}$ | <0.001 $^{***}$ | 0.247 $^{ns}$ |
| Day 10 vs Day 24 | 0.951 $^{ns}$ | 1.000 $^{ns}$ | <0.001 $^{***}$ |

**Table II:** Multiple comparison of mean platelet count at day-1, day-10 & day-24 among different groups of rats (N=30)

| Group | p-value | | |
|---|---|---|---|
| | Day 01 | Day 10 | Day 24 |
| $A_1$ vs $A_2$ vs B | 0.339 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| $A_1$ vs $A_2$ | 0.989 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| $A_1$ vs B | 1.000 $^{ns}$ | <0.001 $^{***}$ | 1.000 $^{ns}$ |
| $A_2$ vs B | 0.458 $^{ns}$ | 1.000 $^{ns}$ | <0.001 $^{***}$ |

Data are expressed as mean ± SD. For statistical analysis one-way ANOVA test was performed for comparison among the groups and then post hoc-Bonferroi test to compare between groups. Figures in parentheses indicate ranges. Group A1 represents the baseline control group, Group A2 is the cyclophosphamide-induced thrombocytopenic control group, and Group B is the experimental group where thrombocytopenic rats were treated with Carica papaya leaf extract. The total number of rats is denoted by N, and the number of rats in each group is denoted by n. Statistical significance is indicated as follows: ns for non-significant, * for significant at p<0.05, and *** for significant at p<0.001

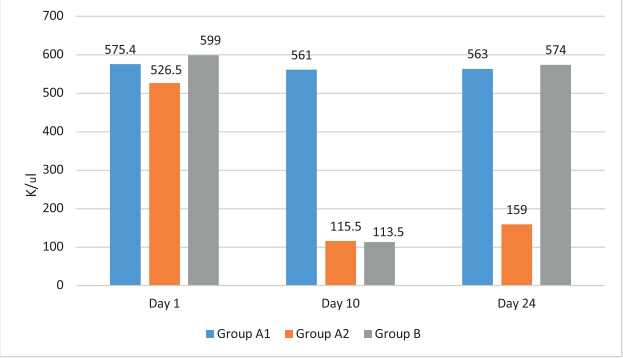



**Figure 2:** Mean platelet count at day-1, day-10 & day-24 in different groups of rats (N=30)

The mean bleeding time on day-1 was 1.98 ± 0.36, 2.18 ± 0.29 and 2.07 ± 0.39 min, on day-10 was 1.89 ± 0.28, 4.30 ± 0.29 and 3.89 ± 0.49 min and on day- 24 was 2.01± 0.20, 4.14 ± 0.46 and 2.17 ± 0.39 min in group A1, group A2 and group B, respectively (Figure 3).

The mean ±SD bleeding time in group A1 was almost similar on day-1, day-10 and day-24 and the differences was not statistically significant. Whereas, in group A2 this level was significantly (p<0.001) increased on day-10 and day-24 in comparison to that of day-1.

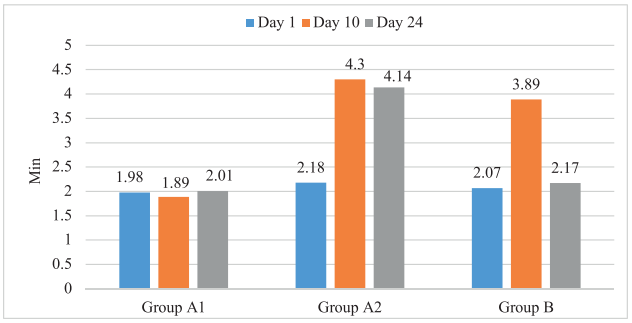



**Figure 3:** Mean bleeding time in different groups of rats (N=30)

Again, The mean ±SD bleeding time in group B was significantly (p<0.001) increased on day-10 than that of day-1. Whereas, this level was significantly (p<0.001) decreased on day-24 than that of day-10. However, this level was almost similar and the differences was not statistically significant between day-1 and day-24 (Table III).

**Table III:** Multiple comparison of mean bleeding time at day 1, day 10 & day 24 within different groups of rats (N=30)

| Group | p-value | | |
|---|---|---|---|
| | Group $A_1$ | Group $A_2$ | Group B |
| Day 1 vs Day 10 | 0.597 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| Day 1 vs Day 24 | 0.787 $^{ns}$ | <0.001 $^{***}$ | 0.446 $^{ns}$ |
| Day 10 vs Day 24 | 0.333 $^{ns}$ | 0.220 $^{ns}$ | <0.001 $^{***}$ |

The mean ± SD bleeding time on day-1 was almost similar in all groups and the differences were not statistically significant. However, on day-10 this level was significantly (p<0.001) higher in group A2 and group B in comparison to that of group A1. Whereas, this level was almost similar and the differences was not statistically significant between group A2 and group B. Again, on day-24 the bleeding time was significantly (p<0.001) higher in group A2 in comparison to that of group A1 and it was significantly (p<0.001) lower in group B in comparison to that of group A2. However, this level was almost similar and the differences was not statistically significant between group A1 and group B (Table IV).

**Table IV:** Multiple comparison of mean bleeding time at day 1, day 10 & day 24 among different groups of rats (N=30)

| Group | p-value | | |
|---|---|---|---|
| | Day 01 | Day 10 | Day 24 |
| $A_1$ vs $A_2$ vs B | 0.450 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| $A_1$ vs $A_2$ | 0.634 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| $A_1$ vs B | 1.000 $^{ns}$ | <0.001 $^{***}$ | 1.000 $^{ns}$ |
| $A_2$ vs B | 1.000 $^{ns}$ | 0.055 $^{ns}$ | <0.001 $^{***}$ |

The mean ±SD clotting time on day-1 was 3.96± 0.35, 4.07± 0.54 and 4.22 ± 0.51min, on 4,18 ± 0. day-10 was 3.94± 0.31, 5.76± 0.44 and 5.99 ± 0.28 min and on day-24 was 4.18 ±0.30, 5.91 ± 0.29 and 4.15 ± 0.44 min in group A1, group A2 and group B respectively (Figure 4).

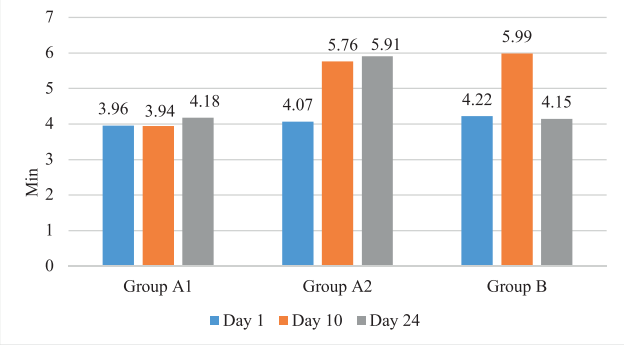



**Figure 4:** Mean clotting time of different groups of rats

The mean ±SD clotting time in group A1 was almost similar on day-1, day-10 and day-24. Whereas, the mean ±SD clotting time in group A2 was significantly (p<0.001) increased on day-10 and day-24 in comparison to that of day-1. Again, the mean ±SD clotting time in group B was significantly (p<0.001) increased on day- 10 than that of day-1. Whereas, it was significantly (p<0.001) decreased on day-24 in comparison to that of day-10. However, clotting time was almost similar and the difference was not statistically significant between day-1 and day-24 (Table V).

**Table V:** Multiple comparison of mean clotting time at day-1,day-10 and day-24 within different groups of rats (N=30)

| Group | p-value | | |
|---|---|---|---|
| | Group A1 | Group A2 | Group B |
| Day 1 vs Day 10 | 0.900 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| Day 1 vs Day 24 | 0.062 $^{ns}$ | <0.001 $^{***}$ | 0.724 $^{ns}$ |
| Day 10 vs Day 24 | 0.081 $^{ns}$ | 0.442 $^{ns}$ | <0.001 $^{***}$ |

The mean ± SD clotting time on day-1 was almost similar in all groups and the differences were not statistically significant. On day-10, this level was significantly (p<0.001) higher in group A2 and in group B in comparison to that of group A1, whereas this level was almost similar and the difference was not statistically significant between group A2 and group B. On day-24, this level was significantly (p<0.001) higher in group A2 in comparison to that of group A1 and it was significantly (p<0.001) lower in group B in comparison to that of group A2. However, this level was almost similar and the difference was not statistically significant in between group A1 and group B.

**Table VI:** Multiple comparison of mean clotting time at day-1,-day-10 and day-24 among different groups of rats (N=30)

| Group | p-value | | |
|---|---|---|---|
| | Day 01 | Day 10 | Day 24 |
| $A_1$ vs $A_2$ | 1.000 $^{ns}$ | <0.001 $^{***}$ | <0.001 $^{***}$ |
| $A_1$ vs B | 0.687 $^{ns}$ | <0.001 $^{***}$ | 1.000 $^{ns}$ |
| $A_2$ vs B | 1.000 $^{ns}$ | 0.462 $^{ns}$ | <0.001 $^{***}$ |

The mean ± SD RBC count was 7.51 ± 1.07, 5.45 ± 0.68 and 8.34 ± 0.79 million/µl, mean WBC count was 8.44 ± 1.04, 5.20 ± 0.79 and 7.83 ± 1.34 K/µl, the mean serum SGPT (ALT) level was 37.60 ± 8.14, 69.50 ± 19.23 and 42.40 ± 6.22 U/L and mean serum creatinine was 0.63 ± 0.20, 0.78 ± 0.19 and 0.55 ± 0.17 mg/dl in group A1, group A2 and group B, respectively (Figure 5& 6).

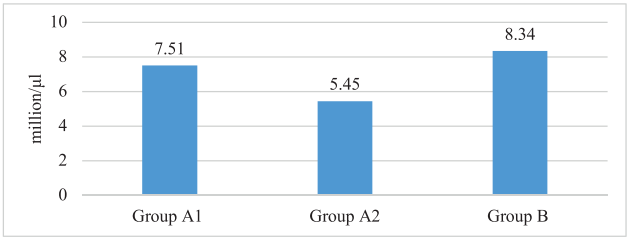



**Figure 5:** Mean RBC count in different groups of rats (N=30)

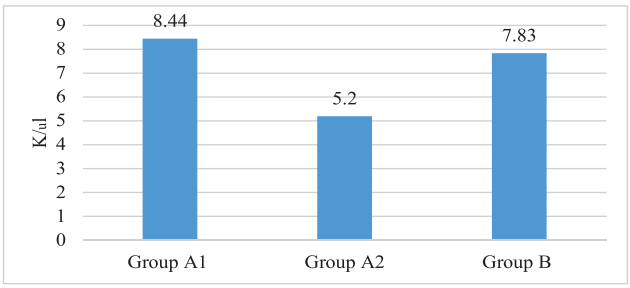



**Figure 6:** Mean WBC count in different groups of rats (N=30)

The mean ±SD RBC count was significantly (p<0.001) higher in group A1 and group B in comparison to that of group A2. Whereas, this level was significantly (p<0.001) higher in group B than that of group A2. Again, this level was almost similar, and the difference was not statistically significant between group A1 and group B. Similarly, the mean ±SD WBC count was significantly (p<0.001) higher in group A1 and in group B in comparison to that of group A2. However, this level was almost similar, and the difference was not statistically significant between group A1 and group B (Table VII).

**Table VII:** Multiple comparison of mean RBC and WBC at day 24 in different groups of rats (N=30)

| Group | p-value | |
|---|---|---|
| | RBC | WBC |
| $A_1$ vs $A_2$vs B | <0.001*** | <0.001*** |
| $A_1$ vs $A_2$ | <0.001*** | <0.001*** |
| $A_1$ vs B | 0.124 ns | 0.653 ns |
| $A_2$ vs B | <0.001*** | <0.001*** |

Statistical analysis was done by Fisher's exact test. Figures in parentheses indicate ranges;

**Discussion**

The present study was carried out to evaluate the antithrombocytopenic effect of C. papaya leaf extract in cyclophosphamide induced thrombocytopenic rats. For the purpose of this study, platelet count, bleeding time and clotting time were done to asses the thrombocytopenic status. Total count of RBC and WBC were performed to see it's effect on blood cells.

Platelet count: In this study, the platelet count in the cyclophosphamide-induced thrombocytopenic control group showed a significant decrease (p<0.001) on both day 10 and day 24 compared to day 1, consistent with findings by8. In contrast, thrombocytopenic rats treated with C. papaya leaf extract exhibited a significant decrease in platelet count on day 10 (p<0.001) compared to day 1, followed by a significant increase by day 24 (p<0.001) compared to day 10, aligning with reports from Dharmarathna et al[18] and Patil et al[15]. Notably, the platelet count in this treated group was statistically similar between day 1 and day 24, although other researchers16 found a significant increase on day 24 compared to day 1. On day 10, platelet counts were significantly lower (p<0.001) in both the cyclophosphamide-induced thrombocytopenic group and the papaya-treated group compared to the baseline control group, corroborating findings from Yan et al[14] and Aster et al[19]. By day 24, the papaya-treated group showed significantly higher platelet counts (p<0.001) than the thrombocytopenic control group. However, no statistically significant difference was observed between the baseline control group and the C. papaya-treated group on day 24, consistent with Sailor et al[20].

In this study, bleeding time (BT) and clotting time (CT) were significantly increased (p<0.001) in the cyclophosphamide-induced thrombocytopenic control group on both day 10 and day 24 compared to day 1, consistent with Patil et al[15]. In the C. papaya leaf-treated group, BT and CT were significantly elevated on day 10 (p<0.001) compared to day 1, followed by a significant decrease on day 24 (p<0.001) compared to day 10, aligning with findings from Nandini et al8 and Anjum et al[16]. No statistically significant difference was observed between day 1 and day 24 in the papaya-treated group, a trend also reported by Sailor et al[20]. On day 10, BT and CT were significantly higher (p<0.001) in both the cyclophosphamide-induced thrombocytopenic control and papaya-treated groups compared to the baseline control group, as observed by Yan et al[14]. By day 24, BT and CT in the papaya-treated group were significantly lower (p<0.001) than in the thrombocytopenic control group. However, Sailor et al[20] reported a slight, non-significant reduction in BT and CT between the papaya-treated and baseline control groups by the end of the study. Similarly, no significant differences were noted between the baseline and papaya-treated groups on day 24, consistent with Patil et al[15].

In this study, on day- 24, RBC count was significantly (p<0.001) higher in thrombocytopenic rats with C. Papaya leaf treated group in comparison to that of cyclophosphamide induced thrombocytopenic control group. Kumar et al[21] also made a similar observation. Whereas, RBC count was almost similar and the differences was not statistically significant between baseline control group and thrombocytopenic rats with C. papaya leaf treated group. Similar findings were also observed by some other researchers[18,20].

In this study, on day 24, the WBC count was significantly lower ($p<0.001$) in the cyclophosphamide-induced thrombocytopenic control group compared to the baseline control group, consistent with findings by Yan et al[14]. In contrast, the C. papaya leaf-treated group showed a significantly higher WBC count ($p<0.001$) than the thrombocytopenic control group, similar to observations by[12]. However, Geetha et al[22] reported no significant change in WBC count in rats treated with C. papaya leaf extract. By day 24, WBC counts in the papaya-treated group and the baseline control group were statistically similar, as also noted by Anjum et al[16].

In the present study, in cyclophosphamide induced thrombocytopenic control group and thrombocytopenic rats with C. papaya leaf treated group, thrombocytopenia induced by cyclophosphamide which is evidenced by low platelet count prolong bleeding time and clotting time.

Conversely, increased level of platelet count, decreased level of BT, CT, higher level of RBC, WBC count in the thrombocytopenic rats with C. papaya leaf treated group indicate that C. papaya leaf has anithrombocytopenic effect.

## Conclusion

The study concludes that C. papaya leaf extract effectively improves thrombocytopenic conditions in Long Evan's male rats induced with cyclophosphamide. For future research, it is recommended to explore the effects of varying doses of C. papaya leaf extract and to investigate the impact of different bioactive compounds within the extract.

**Conflict of interests:** None

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Original Article

# The Effect of Non -Motor Symptoms on Quality of Life of Idiopathic Parkinson's Disease Patient Attending in A Tertiary Level Hospital

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## Abstract

**Background:** Non-motor symptoms (NMSs) are highly prevalent in Parkinson's disease (PD), affecting up to 90% of patients and contributing significantly to reduced quality of life (QoL), even from the early stages of the disease.

**Objective:** To evaluate the impact of NMSs on the QoL in patients with idiopathic PD.

**Methodology:** This cross-sectional study was conducted at the Department of Neurology, BSMMU, from October 2019 to September 2020. A total of 76 patients with idiopathic PD and NMSs were recruited through purposive sampling from the Movement Disorder Clinic, and Inpatient and Outpatient services. Data were collected through clinical assessment, history, and medical records. QoL was assessed using the validated Bengali version of WHOQOL-BREF, while NMSs were evaluated using the 30-item Parkinson's Disease Questionnaire (PDQ-30). Statistical analysis was performed using SPSS.

**Results:** Most participants (65%) were over 50 years old, with 57% in Hoehn and Yahr stages 2–3. NMSs were present in nearly all patients. The most common symptoms included nervousness (78%), fatigue (78%), insomnia (75%), dizziness (68%), mood disturbances (67%), forgetfulness (59%), pain (57%), altered sexual interest (49%), constipation (38%), dysphagia (20%), and excessive sweating (18%). Significant positive correlations were observed between Hoehn and Yahr stage and all QoL domains. Disease duration was significantly associated with sleep/fatigue, attention/memory, and gastrointestinal issues. Inter-domain correlations were also noted, particularly involving mood, cognition, and autonomic symptoms.

**Conclusion:** NMSs are prevalent and strongly impact the quality of life in PD patients. Addressing these symptoms is essential for improving patient well-being and disease management.

**Key words:** Non-Motor Symptoms (NMSs), Quality of Life (QoL), Parkinson's disease (PD)

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## Introduction

Parkinson's Disease represents the second neurodegenerative disorder in the world after Alzheimer's disease with an estimated prevalence of 3% in the elderly and overall 0.3% of population is affected.[1-3] This condition, is caused by degeneration of the dopaminergic neurons of the substantia nigra in the midbrain, is associated with motor symptoms like bradykinesia, rest tremor, rigidity and postural instability and various non motor sympyoms.[4] The hallmark is bradykinesia, leading to slow gait, difficulty standing from sitting, small stride length, reduced arm swing, rigidity in

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trunk movements, propulsion and retropulsion.[5]

Non-motor symptoms (NMSs) include neuropsychiatric features (anxiety, depression, apathy, hallucinosis/ psychosis) sleep disturbance and hypersomnolence, fatigue, pain, sphincter disturbance and constipation, sexual problems (erectile failure, loss of libido or hypersexuality), drooling and weight loss.[6-8] Cognitive impairment, including dementia is the symptom most likely to impair quality of life for patients and their careers. These symptoms constitute a burden on the caregiver and the public health system. In the PRIAMO study, up to 98.6% of PD patients had NMS. Recently, the correlation between NMS and PD patients' health-related quality of life (HRQoL) has been emphasized.9 Several studies indicate that NMS, rather than motor symptoms, are a major cause of poor health related quality of life (HRQoL).[10-11]

Recently, two complementary instruments to assess non-motor symptoms in PD have been developed: The Non Motor Symptoms Questionnaire (NMS Quest)[12] and the Non motor Symptoms Scale (NMSS).[13] The NMS screening questionnaire (NMS Quest), a self-completed questionnaire comprising 30 items, used as rapid screening tool, for the early detection of patient's non-motor symptoms (NMSs).[14-15] Also NMSs is used for NMS burden assessment. Several studies have compared non-motor symptoms (NMS) in different countries and showed more prevalent gastrointestinal symptoms in Asian countries, probably due to ethnic and economic differences.[16-17]

NMS has a deep impact on PD patients' quality of life.[14] The purpose of my study is to investigate NMS in PD patients attending in Neurology department BSMMU and the impact of NMS on HRQOL. This hospital-based cross-sectional study was conducted to examine the clinical factors, on the occurrence of non-motor symptoms (NMSs) and health related quality of life (HRQOL). 30-item Parkinson's Disease Questionnaire (PDQ-30) and Validated Bengali version of WHOQOL-BREF17 were used to explore the correlation.

**Materials and methods**

This cross-sectional study was conducted in the movement disorder clinic, outpatient and in patient department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka over a period one year from October 2019 to September 2020. A total of 76 patients diagnosed as idiopathic Parkinson's disease with non-motor symptoms was taken as study population. Patients with anti-psychotic drug induced NMSs, secondary cause of parkinsonism, those who will not provide consent and atypical Parkinson's disease were excluded from the study. Approval from the Institutional Review Board (IRB) of BSMMU was obtained prior to the commencement of this study. Idiopathic Parkinson's Disease patients were diagnosed on brain bank criteria. Parkinson's disease of patient was selected from movement disorder clinic, outpatient and inpatient Department of Neurology of BSMMU. After taking proper history, physical and neurological examinations and relevant investigations were done. Informed written consent was taken from each patient. After diagnosis of idiopathic Parkinson's disease detected by non-motor symptoms assessment scale (developed by the international Parkinson's disease non-motor group) Quality of life in idiopathic Parkinson's disease detected by who quality of life scale. Proper diagnosis and treatment were ensured for each patient. Collected data were compiled and appropriate analyses were done by using computer-based software, Statistical Package for Social Sciences (SPSS) version 23.0. Qualitative variables were expressed as percentage and quantitative variables as median or mean. Pearson's correlation coefficient was calculated between Hoehn and Yahr stage with total Score Domain and Pearson's correlation coefficient was calculated between Diseases duration vs Nonmotor Symptom Domain 1 to Domain 6. A 'p' value of $<0.05$ was considered as significant.

**Results**

Out of 76 patients, among the patients highest (27.6%) were in the age group between 61 to 70 years of age and the lowest (2.6%) were in the age group of 81 to 90 years. The age mean and standard deviation (±SD) of the patients were 3.25 ±1.45 years. Among the patients most of them (72.4%) were male and the rest of (27.6%) were female. Among the 76 patients most of them (64.5%) treatment duration was between 1 to 4 years and the lowest (5.3%) diseases duration were below one year (Table-I). Among the patients score highest (42.11%) Hoehn and Yahr stage (score) were 2 followed by (39.37%) were 1 and lowest (3.94%)

were 0 (Figure-1). In domain 1 among the patients score highest (68.4%) dizziness score was >1 and highest (93.4%) fall score were zero (0). In domain 2 among the patients score highest (73.7%) daytime sleep score was zero (0) and highest (75%) Difficulties fall and staying sleep score were >1 and highest (59.2%) were restless in legs score were zero (0). The following table 11 shows in detail (Table-II). In domain 3 among the patients score highest (59.2%) lots of interest in his/her surroundings score were zero (0) and highest (65.8%) Loss of interest in new activities score were >1 and highest (77.7%) feeling of nervous score were >1 and highest (62.4%) depressed mood score was >1 and highest (61.8%) flat mode score was >1 and highest (59.2%) lack of pleasure score were >1 (Table-III). In domain 4 among the patients score highest (90.8%) see the things are not there/hallucination score were zero (0) and highest (92.1%) belief that you are not real/delusions score were zero (0) and highest (88.2%) double vision score was zero (0). In domain 5 among the patients score highest (50%) Problem of concentration driving activities score was zero (0) and highest (59.2%) Short term memory lost score were >1 (Table-IV). Positive significant correlation (r=0.409; p=0.001) was found between Hoehn and Yahr stage (score) and Total Score Domain 1 to Domain 9 (Table-V). A positive significant correlation was found between diseases duration of the patients and Domain 2: Sleep/fatigues (r=0.227; p=0.049). A positive significant correlation was found between Domain 1: Cardiovascular including falls and Domain 2: Sleep/fatigues (r=0.257; p=0.025) and Domain3: Mood/cognition (r=0.328; p=0.004) (Table-VI). A positive significant correlation was found between diseases duration of the patients and Domain 5: Attention/memory (r=0.315; p=0.006) and Domain 6: Gastrointestinal tract (r=0.316; p=0.005). A positive significant correlation was found between Domain 4: Perceptual problem and Domain 5: Attention/memory (r=0.225; p=0.026). Positive significant correlation was found between Domain 5: Attention/memory and Domain 6: Gastrointestinal tract (r=0.352; p=0.002) (Table-VII).

**Table I:** Distribution of the patients by baseline characteristics

| Baseline characteristics | Number | Percentage | Mean±SD |
|---|---|---|---|
| **Age (years)** | | | |
| 31 to 40 | 7 | 9.2 | 3.25±1.45 |
| 41 to 50 | 20 | 26.3 | |
| 51 to 60 | 16 | 21.1 | |
| 61 to 70 | 21 | 27.6 | |
| 71 to 80 | 7 | 9.2 | |
| 81 to 90 | 2 | 2.6 | |
| 21 to 30 | 3 | 3.9 | |
| Total | 76 | 100.0 | |
| **Sex** | | | |
| Male | 55 | 72.4 | |
| Female | 21 | 27.6 | |
| Total | 76 | 100.0 | |
| **Treatment duration** | | | |
| Below 1 Year | 4 | 5.3 | |
| (1 to 4) Years | 49 | 64.5 | |
| (5 to 14) Years | 23 | 30.3 | |
| Total | 76 | 100.0 | |

**Table II:** Domain 1: Cardiovascular including falls (score) and Domain 2: Sleep/fatigues

| Variables | Range | | Frequency | Percentage |
|---|---|---|---|---|
| **Domain 1** | | | | |
| Dizziness Score | Valid | 0 | 24 | 31.8 |
| | | ≥1 | 52 | 68.4 |
| | | Total | 76 | 100.0 |
| Fall Score | | 0 | 71 | 93.4 |
| | | ≥1 | 5 | 6.6 |
| | | Total | 76 | 100.0 |
| **Domain 2** | | | | |
| Daytime sleep | | 0 | 56 | 73.7 |
| | | ≥1 | 20 | 26.3 |
| | | Total | 76 | 100.0 |
| Difficulties fall and staying sleep | | 0 | 19 | 25 |
| | | ≥1 | 57 | 75 |
| | | Total | 76 | 100.0 |
| Restless in legs | | 0 | 31 | 59.2 |
| | | ≥1 | 45 | 40.8 |
| | | Total | 76 | 100.0 |

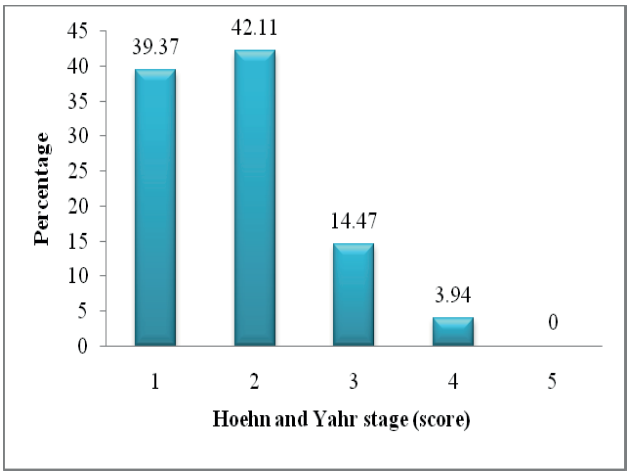



**Figure 1:** Hoehn and Yahr stage (score)

**Table III:** Domain 3: Mood/cognition

| Variables | | Range | Frequency | Percentage |
|---|---|---|---|---|
| Loss of interest in his/her surroundings score | Vali d | 0 | 45 | 59.2 |
| | | ≥1 | 31 | 40.8 |
| | Tota l | | 76 | 100.0 |
| Loss of interest in new activities | | 0 | 26 | 34.2 |
| | | ≥1 | 50 | 65.8 |
| | Tota l | | 76 | 100.0 |
| Feeling of nervousness | | 0 | 17 | 22.3 |
| | | ≥1 | 59 | 77.7 |
| | Tota l | | 76 | 100.0 |
| Depressed mood | | 0 | 21 | 27.6 |
| | | ≥1 | 55 | 62.4 |
| | Tota l | | 76 | 100.0 |
| Flat mode | | 0 | 29 | 38.2 |
| | | ≥1 | 47 | 61.8 |
| | Tota l | | 76 | 100.0 |
| Lack of pleasure | | 0 | 31 | 40.8 |
| | | ≥1 | 45 | 59.2 |
| | Tota l | | 76 | 100.0 |

**Table IV:** Domain 4: Perceptual problem & Domain 5: Attention/memory

| Variables | | Range | Frequency | Percentage |
|---|---|---|---|---|
| **Domain 4** | | | | |
| See the thing are not there/Hallucination | Valid | 0 | 69 | 90.8 |
| | | ≥1 | 7 | 9.2 |
| | Tota l | | 76 | 100.0 |
| Belief that you are not real/Delusions | | 0 | 70 | 92.1 |
| | | ≥1 | 6 | 7.9 |
| | Tota l | | 76 | 100.0 |
| Double vision | | 0 | 67 | 88.2 |
| | | ≥1 | 9 | 11.8 |
| | Tota l | | 76 | 100.0 |
| **Domain 5** | | | | |
| Problem of concentration driving activities | | 0 | 38 | 50 |
| | | ≥1 | 38 | 50 |
| | Tota l | | 76 | 100.0 |
| Short term memory lost | | 0 | 31 | 40.8 |
| | | ≥1 | 55 | 59.2 |
| | Tota l | | 76 | 100.0 |

**Table V:** Hoehn and Yahr stage with total Score Domain Correlations

| Description | | Hoehn and Yahr stage (score) | Total Score Domain 1 to Domain 9 |
|---|---|---|---|
| Hoehn and Yahr stage (score) | Pearson Correlation | 1 | .409** |
| | Sig. (2-tailed) | | .000 |
| | N | 76 | 76 |
| Total Score Domain 1 to Domain 9 | Pearson Correlation | .409** | 1 |
| | Sig. (2-tailed) | .000 | |
| | N | 76 | 76 |

**. Correlation is significant at the 0.01 level (2-tailed).

**Table VI:** Diseases duration vs Nonmotor Symptom Domain 1 to Domain 3 Correlations

| Description | | Diseases duration of the patients | Domain 1: Cardiovascular including falls (score) | Domain 2: Sleep/fatigues | Domain3: Mood/cognition |
|---|---|---|---|---|---|
| Diseases duration of the patients | Pearson Correlation | 1 | .064 | .227* | -.077 |
| | Sig. (2-tailed) | | .584 | .049 | .506 |
| | N | 76 | 76 | 76 | 76 |
| Domain 1: Cardiovascular including falls (score) | Pearson Correlation | .064 | 1 | .257* | .328** |
| | Sig. (2-tailed) | .584 | | .025 | .004 |
| | N | 76 | 76 | 76 | 76 |
| Domain 2: Sleep/fatigues | Pearson Correlation | .227* | .257* | 1 | .070 |
| | Sig. (2-tailed) | .049 | .025 | | .550 |
| | N | 76 | 76 | 76 | 76 |
| Domain3: Mood/cognition | Pearson Correlation | -.077 | .328** | .070 | 1 |
| | Sig. (2-tailed) | .506 | .004 | .550 | |
| | N | 76 | 76 | 76 | 76 |

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

**Table VII:** Diseases duration vs Nonmotor Symptom Domain 4 to Domain 6 Correlations

| Description | | Diseases duration of the patients | Domain 4: Perceptual problem | Domain 5: Attention/memory | Domain 6: Gastrointestinal tract |
|---|---|---|---|---|---|
| Diseases duration of the patients | Pearson Correlation | 1 | -.034 | .315** | .316** |
| | Sig. (2-tailed) | | .771 | .006 | .005 |
| | N | 76 | 76 | 76 | 76 |
| Domain 4: Perceptual problem | Pearson Correlation | -.034 | 1 | .255* | .116 |
| | Sig. (2-tailed) | .771 | | .026 | .320 |
| | N | 76 | 76 | 76 | 76 |
| Domain 5: Attention/memory | Pearson Correlation | .315** | .255* | 1 | .352** |
| | Sig. (2-tailed) | .006 | .026 | | .002 |
| | N | 76 | 76 | 76 | 76 |
| Domain 6: Gastrointestinal tract | Pearson Correlation | .316** | .116 | .352** | 1 |
| | Sig. (2-tailed) | .005 | .320 | .002 | |
| | N | 76 | 76 | 76 | 76 |

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

**Table VII:** Diseases duration vs Nonmotor Symptom Domain 7 to Domain 9 Correlations

| Description | | Diseases duration of the patients | Domain 7: Urinar | Domain 8: Sexual function | Domain 9: Miscellaneous |
|---|---|---|---|---|---|
| Diseases duration of the patients | Pearson Correlation | 1 | .137 | -.002 | .120 |
| | Sig. (2-tailed) | | .238 | .990 | .304 |
| | N | 76 | 76 | 76 | 76 |
| Domain 7: Urinary | Pearson Correlation | .137 | 1 | .094 | .275* |
| | Sig. (2-tailed) | .238 | | .417 | .016 |
| | N | 76 | 76 | 76 | 76 |
| Domain 8: Sexual function | Pearson Correlation | -.002 | .094 | 1 | .024 |
| | Sig. (2-tailed) | .990 | .417 | | .834 |
| | N | 76 | 76 | 76 | 76 |
| Domain 9: Miscellaneous | Pearson Correlation | .120 | .275* | .024 | 1 |
| | Sig. (2-tailed) | .304 | .016 | .834 | |
| | N | 76 | 76 | 76 | 76 |

*. Correlation is significant at the 0.05 level (2-tailed).

**Discussion**

Parkinsons Disease affect about 1-2% of the population over 65 years of age & up to 3-5% of people 85 years of age & older.[18] The results show a high prevalence of NMSs in our patients, in whom at least one NMS has been found. The results are NMSs prevalence rate of 100%. Other study NMSs of Parkinsons disease and impact on quality of life in Moroccan patients also prevalence rate of 100%.[19-20] The total patients of study were 76 whereas male were 55(72.4%) and female were 21 (27.6%). In another study conducted in Thailand, there was 76% respondent was male and rest of them are female. The age of the patients was above 50 years (>64.5%) and below 50 years (35.5%). This finding is similar to the study finding of Li et al.[19]

Among the 76 patients most of them (64.5%) treatment duration was between 1 to 4 years and the lowest (5.3%) disease duration below one year. Longer disease duration, advanced disease, longer levodopa use, and higher daily dose are associated with the higher occurrence of non-motor symptoms of PD.[9,21-22] This study's Hoehn and Yahr stage 2 to 3 is 56.58% and stage 1 is 39.37%. Previous study showed the predominant population in stage 2 to 3.[23]

In this study the most frequent NMSs were dizziness, mood or cognition impairment, difficulties falling and staying sleep and feelings of pain. The urinary disturbances were the most frequent NMSs in previous studies.[10] But other study sleep and mood/cognition disorder were found in 88.3% and 80.6% of the patients, constituting the non-motor symptoms with the greatest impact on quality of life.[24]

In domain 1 among the patients score highest (68.4%) dizziness score and lowest score 6.6% were fall. Almost similar symptoms of dizziness were present in more than half of patients.[25] In domain 2 there were difficulties falling and staying sleep up to 75% and daytime sleep up to 26.3% participants. Where sleep disorders are more frequent NMSs up to 90% of people with PD.[26-27] This study was restless in legs up to 40.8%. Previous studies 8 to 20 % participants were RLS.[28]

In domain 3 among the patients were cognition/mood more Markley effect such as feeling of nervousness 77.7%, loss of interest in new activities 65.8%, depressed mood 62.4%, flat mode 61.[8]

% lack of pleasure 59.2% and loss of interest in his/her surroundings 40.8%. Cognitive dysfunction affects 24% of patients with newly diagnosed PD.[29] Other previous studies 44.7-54% was cognitive impairment.[9,22]

However, 63% of our patients admitted having cognitive problems only at slight or mild level. The correlation between cognitive impairment and QoL in patients with PD has been well-established.[30-31]

In domain 4 among the patients' perceptual problems/ hallucinations were up to 9%. But the previous study was up to one third of patients suffer from hallucination chronically treatment PD patients.[32] In domain 5 among the patients were forgetfulness up to 59.2% and loss of concentration 50%. Another study also found that participants with attentional/ memory deficits reported an increased PD-39 scores.[9]

In this study in domain 6 were constipation 38.2%, difficulty in shallow 19.7% and dribbling of saliva 11.8%. In a previous study constipation was the most common symptom and swallowing difficulties were around 20%.[9,14].

In domain 7 among the patients were urinary frequency 44.7%, urgency 43.4% and nocturia 34.2%. The most frequent NMSs were the urinary disturbances, which is in line with several previous studies.[10]

In domain 8 among the patients were altered interest in sex 48.5% and problem having sex 27.6%. We trivialize the existing troubles and relate them to their advanced age. In a previous study reported that the question relating to sex were frequently left unanswered.14 In domain 9 among the patients were pain 56.6%, smell disturbance 45.7%, excessive sweating (not related to hoy weather)18.4% and change in weight (not related to dieting) 15.8%.

Previous study was pain affects up to 74% of PD patients and due to its heterogenous etiology, presents a complex diagnostic and management issue.[33] Regarding olfactory disorders, they exist in a large majority of PD patients (up to 90%) and most often are present at the time of diagnosis. Overall, the relative NMSs occurrence, as evaluated by NMS-30 is consistent dizziness (68.4%), mood/cognition (67%), difficulties falling sleep (75%), restless leg (40.8%) and urinary symptoms 40%. Though, in more than 70% of cases, patients are unaware of their smell changes. Previous study there is a paucity of work examining the impact of sweating on QoL in PD despite studies showing that it affects almost half of the patients.[34]

In this study there was Pearson correlation between Hoehn and Yahr symptoms with non-motor symptoms domains 1 to 9. Most of the correlations were significant (<0.05). NMSs have considerable correlation with PDQ-39 scores with p value being significant like that observed in study with p value of (0.000).[10,35] This study's disease duration vs non-motor symptom were Pearson correlation and most of domain were significant (<0.05). Retrospective study with a long mean duration from PD diagnosis of 7.6±5.6 years, reported 98.9% of subjects experienced prodromal symptoms preceding a diagnosis of PD similar.[36]

Hoehn and Yahr stage vs QoL were Pearson correlation also significant (<0.05). The Hoehn and Yahr stage correlated more strongly with QoL scores than the motor part of the UPDRS.[37]. Identifying the specific patterns of NMSs occurrence concerning time of symptoms has been pivotal in understanding the evolution and its contribution to disease morbidity of PD individuals. Routine assessment of NMSs by using simple Questionnaires like NMSs quest and their impact on life by using PDQ-30, PDQ-39, PDQ-8 and Hoehn and Yahr scoring.[23]

Several limitations exist to the present study, the sample size was small (worth mentioning the COVID-19 situation which severely hampered sample collection), tt was single centered, study period was short, no further follow up was done, comorbid neurologic disorder were not assessed, motor symptoms also hampered the quality of life and control group was no consideration.

**Conclusion**

In this study we observed significant association of non–motor symptom with QoL NMSs are common in patients with PD, although they are often overlooked. NMSs result in a significant burden for people with PD and negatively affect QoL. Further studies are needed to assess the effect of treating NMSs on improving QoL.

**Conflict of interests:** None

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In domain 7 among the patients were urinary frequency 44.7%, urgency 43.4% and nocturia 34.2%. The most frequent NMSs were the urinary disturbances, which is in line with several previous studies.[10]

In domain 8 among the patients were altered interest in sex 48.5% and problem having sex 27.6%. We trivialize the existing troubles and relate them to their advanced age. In a previous study reported that the question relating to sex were frequently left unanswered.14 In domain 9 among the patients were pain 56.6%, smell disturbance 45.7%, excessive sweating (not related to hoy weather)18.4% and change in weight (not related to dieting) 15.8%.

Previous study was pain affects up to 74% of PD patients and due to its heterogenous etiology, presents a complex diagnostic and management issue.[33] Regarding olfactory disorders, they exist in a large majority of PD patients (up to 90%) and most often are present at the time of diagnosis. Overall, the relative NMSs occurrence, as evaluated by NMS-30 is consistent dizziness (68.4%), mood/cognition (67%), difficulties falling sleep (75%), restless leg (40.8%) and urinary symptoms 40%. Though, in more than 70% of cases, patients are unaware of their smell changes. Previous study there is a paucity of work examining the impact of sweating on QoL in PD despite studies showing that it affects almost half of the patients.[34]

In this study there was Pearson correlation between Hoehn and Yahr symptoms with non-motor symptoms domains 1 to 9. Most of the correlations were significant (<0.05). NMSs have considerable correlation with PDQ-39 scores with p value being significant like that observed in study with p value of (0.000).[10,35] This study's disease duration vs non-motor symptom were Pearson correlation and most of domain were significant (<0.05). Retrospective study with a long mean duration from PD diagnosis of 7.6±5.6 years, reported 98.9% of subjects experienced prodromal symptoms preceding a diagnosis of PD similar.[36]

Hoehn and Yahr stage vs QoL were Pearson correlation also significant (<0.05). The Hoehn and Yahr stage correlated more strongly with QoL scores than the motor part of the UPDRS.[37]. Identifying the specific patterns of NMSs occurrence concerning time of symptoms has been pivotal in understanding the evolution and its contribution to disease morbidity of PD individuals. Routine assessment of NMSs by using simple Questionnaires like NMSs quest and their impact on life by using PDQ-30, PDQ-39, PDQ-8 and Hoehn and Yahr scoring.[23]

Several limitations exist to the present study, the sample size was small (worth mentioning the COVID-19 situation which severely hampered sample collection), tt was single centered, study period was short, no further follow up was done, comorbid neurologic disorder were not assessed, motor symptoms also hampered the quality of life and control group was no consideration.

**Conclusion**

In this study we observed significant association of non–motor symptom with QoL NMSs are common in patients with PD, although they are often overlooked. NMSs result in a significant burden for people with PD and negatively affect QoL. Further studies are needed to assess the effect of treating NMSs on improving QoL.

**Conflict of interests:** None

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**Original Article**

# Relationship Between Resting Pulse Pressure and Left Ventricular Diastolic Dysfunction in Hypertensive Patients

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## Abstract

**Background:** The prevalence of hypertension in adults is much higher all over the world as well as in Bangladesh . Left ventricular (LV) diastolic dysfunction is first discernible manifestation of cardiac disease in hypertensive patients. Left ventricular (LV) diastolic dysfunction is associated with increased morbidity and mortality in a patient with Systemic Hypertension. This study observed the relationship between pulse pressure in rest as a clinical marker with the LV diastolic dysfunction found on Echocardiography.

**Methods:** This was an observational analytical study. Here consecutive convenience sampling of hypertensive patients was done without the other conditions that affect pulse pressure and left ventricular diastolic function. Data were collected by observing their measurement of resting blood pressure and the findings of LV diastolic dysfunction in echocardiography. Results were analyzed accordingly in SPSS.

**Results:** In total, 118 patients (97 M, 21 F), mean age 50 years, ranging from 31-68 years with systemic arterial hypertension were studied. Among them, 75(63.6%) had left ventricular diastolic dysfunction and 43(36.4%) had normal diastolic function. They were divided into three group of tertiles according to their Pulse Pressure (PP). The highest tertile (the third tertile) of PP group of patients had a significantly higher diastolic dysfunction (5% vs 95%; P=0.0001).

**Conclusion:** This study may help to predict LV diastolic dysfunction early by simple clinical knowledge of pulse pressure during routine clinical measurement of blood pressure in hypertensive patients. LV diastolic dysfunction is a marker of cardiovascular disability including mortality and morbidity. So, early detection of LV diastolic dysfunction will be possible clinically & ultimately it will reduce mortality and morbidity.


**Key words:** Pulse pressure, Diastolic dysfunction, Hypertension, Echocardiography.

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## Introduction

The prevalence of hypertension in adults all over the world is increasing day by day. In Bangladesh overall prevalence rates of systolic and diastolic hypertension in the study population were 14.4 and 9.1 percent respectively.[1] Arterial stiffness is a strong marker of vascular damage and is closely associated with atherosclerotic cardiovascular diseases & LV diastolic disorder especially in patients with essential hypertension.[2] One of the noninvasive indices of arterial stiffness such as pulse pressure (difference between systolic & diastolic pressure) have been shown to predict cardiovascular outcomes.[3] Left ventricular diastolic dysfunction is the first discernible manifestation of cardiac disease in hypertensive patients.[4] The prevalence of left ventricular diastolic dysfunction in hypertension has been well documented. This ranges from 46 to 68% in various studies in Caucasians.[5] The estimated annual mortality due to diastolic dysfunction varies widely from 9-28% in several studies. Left ventricular (LV) diastolic dysfunction

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has been shown to be increasingly prevalent with advancing age and although most frequently found in the preclinical phase of disease, is a predictor of all-cause mortality.[7] The diastolic phase of the cardiac cycle is divided into the isovolumic relaxation period and three filling phases. Several Echocardiographic parameter including transmitral pulse wave Doppler & mitral annular tissue Doppler tracing can show the evidences of LV diastolic dysfunction.[8] Higher pulse pressures have been correlated with an increased occurrence of cardiovascular events.[9] In a large cross-sectional prospective study by Benetos et al. (1997) and others of 19,083 patients 40 to 69 years of age, the pulse pressure alone was shown to be an independent predictor of cardiac risks as judged by the degree of cardiac hypertrophy and LV diastolic dysfunction.[10]

This study was conducted to find out the relationship between pulse pressure and left ventricular diastolic dysfunction by echocardiography in hypertensive patients. In Bangladesh, we have limited investigational facilities particularly in rural area. So most of the physicians have to access the patient clinically. Hypertensive patients may develop LV diastolic dysfunction very early and patients remain asymptomatic. LV diastolic dysfunction is assessed by Echocardiography with Doppler study. So, the large hypertensive population might be benefited by reducing investigation cost and taking appropriate referral from the physician for further evaluation & management. So it was very rational to find out clinical clue of LV diastolic dysfunction in hypertensive patient by pulse pressure that help early detection.

**Methods**

This prospective observational study was done in University cardiac center, Bangladesh Medical University (BMU) from December 2010 to September 2011 and July-December, 2023. Hypertensive Patients (diagnosed according to definition of JNC-7). Sample Size: Minimum 84(eighty four).[11] At first total 118 were taken by Sample size equation for hypothesis testing, the equation of difference between two proportions and 90 patient were studied for principal findings in 2023. The proposed study protocol was approved by the ethical committee of BMU. Study Procedure: Hypertensive patients who had come in BMU cardiology department for Echocardiography through outpatients, inpatients and emergency department fulfilling the inclusion criteria were enrolled. A total 146 patients were examined & out of them 28 patients were excluded by exclusion criteria. Initial evaluation of the patients was done by detailed history, clinical examination and relevant investigations. All relevant data were collected and recorded in a predesigned data collection format. Inclusion criteria: Patients had included in the study after obtaining informed consent. All patients diagnosed as a case of hypertension with Newly detected & without any antihypertensive medication. Exclusion criteria: Cases with Well controlled Hypertension by drugs, known cases of secondary hypertension, other known factors that affects blood pressure, Patients refusal to include in this study. At first portion total 118 patients finally included in this study according to inclusion and exclusion criteria. In 2023, total 90 patient studied accordingly. They were divided into three group according to their tertiles of pulse pressure[12]. The first tertile included the patients with pulse pressure below 53 mm of Hg, the second with pulse pressure between 53-70, mm of Hg, the third with pulse pressure above 70 mm of Hg. Blood Pressure Measurement: Blood pressure was measured in seated position after 5 minutes rest in every included patients according to guideline of office blood pressure measurement of JNC-7[13], Echocardiographic measurements: Recordings were taken with patients in the left lateral decubitus position. M mode tracings were recorded at a speed of 50 mm/s and the Doppler signals at 100 mm/s. Color Doppler and Tissue Doppler were used to measure the diastolic dysfunction of the patient, according to the standard criteria recommended by the American Society of Echocardiography to diagnose diastolic dysfunction.[14] Echocardiographic Assessment of Diastolic Function: Evaluation of diastolic function consists of assessing myocardial relaxation, filling pressures, and left ventricular (LV) compliance. Both two-dimensional and Doppler echocardiography was used noninvasively to assess diastolic function.

Reduced motion of the mitral annulus, increased left atrial size, and frequently increased LV wall thickness was observed and noted. Diagnosis of Left ventricular diastolic

dysfunction was made mainly on the basis of results of the mitral inflow pattern, pulmonary vein Doppler velocities, tissue Doppler imaging of the mitral annulus, and color flow imaging of mitral inflow.

Categorical data were expressed as frequencies and corresponding percentages. Continuous variables were summarized as group or as mean ± SD. Differences between discrete variables were analyzed for significance by the chi-square test. As regard to continuous variables, the ANOVA model was used to assess significance of difference. From the test, the P-value was obtained using standard statistical tables. For multiple comparisons, a P-value <0.05 was considered statistically significant. The data processing and statistical analysis was done using SPSS (statistical package for social science) 16.0 statistical program.

**Results**

In total, 118 patients (97 M, 21 F), mean age 50 years, ranging from 31-68 years, with arterial hypertension were enrolled in the study group according to the inclusion and exclusion criteria. Based on their echocardiograhic assessment, total 75(63.6%) had diastolic dysfunction & 43(36.4%) had normal diastolic function. They were divided into tertiles according to resting Pulse Pressure (PP). The first tertile included the patients with PP below 53 mm of Hg, the second those with PP between 53-70, mm of Hg, the third with PP above 70 mm of Hg. The highest tertile (the third tertile) of PP group of patient had a significantly higher diastolic dysfunction (5% vs 95%; P=0.0001).

**Table 1:** Baseline demographic characteristics of the patients ccording to the tertiles of pulse pressure (PP) (n=118).

| Characteristics | !st tertiles of PP | 2nd tertiles of PP | 3rd tertiles of PP | P value |
|---|---|---|---|---|
| Age ( M±SD) | 44±6 | 50.6±6.8 | 53.3±9.8 | <0.001 |
| Male n (%) | 33(84%) | 28(71%) | 36(91%) | =0.07 |
| Female n(%) | 6(15.6%) | 11(29%) | 4(9%) | |
| BMI (Kg/m$^2$ ) ( M±SD) | 24.4±2 | 25.6±2.2 | 24.5±1.9 | =0.07 |

Baseline demographic characteristics of patients in each group according to the tertiles of pulse pressure revealed no significant differences. Only Age of the Patients was significantly higher in higher pulse pressure group. Most of the baseline clinical characteristics were not significantly differ from one group to another except the value of blood pressure measurement. The nean pulse pressure of 1st, 2nd, 3rd tertiles group were 44, 64, 79 mm of Hg. Echocardiographic parameters during the assessment of the diastolic dysfunction showed that most of the parameters had significant difference among the tertiles of the pulse pressure group.

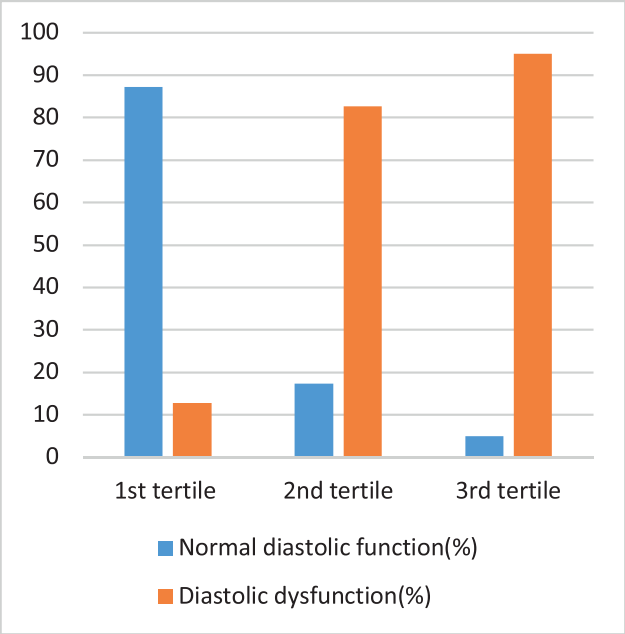
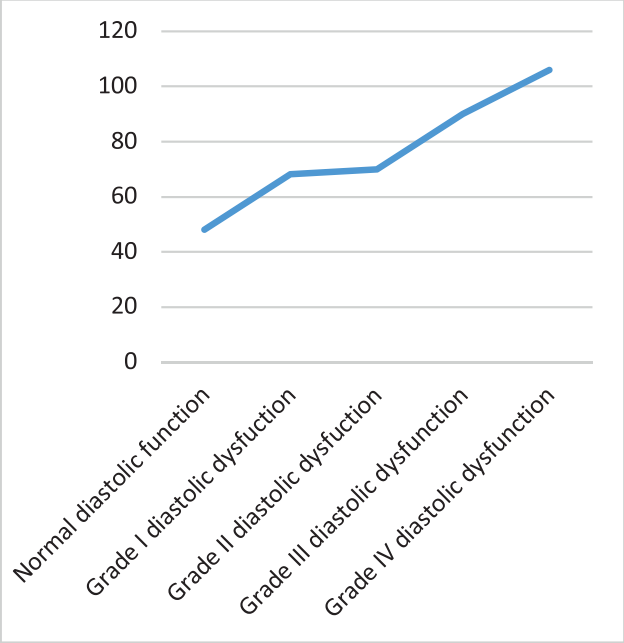



**Figure-1:** Bar diagram shows the proportion of diastolic dysfunction in this study patients according to the tertiles of pulse pressure.(n=118).

(X-axis represents proportion of diastolic dysfunction and Y-represent pulse pressure group.) 1 tertile (Pulse pressure <53 mm of Hg), 2nd tertile (Pulse pressure between 53-69 mm of Hg), 3rd tertile (Pulse pressure >70 mm of Hg). 1" tertile group(n=39) had 34(87.2%) normal and 5(12.8%) diastolic dysfunction, 2nd tertile group(n=39) had 7(17.3%) normal and 32(82.1%) diastolic dysfunction, 1" tertile group(n=40) had 2(5%) normal and 38(95%) diastolic dysfunction.




*Vertical axis shows mean pulse pressure

**Figure-2:** Mean plot graph (Line graph) showing the Pulse pressure and mean pulse pressure of different grades of diastolic dysfunction.

(X-axis represents the different grades of LV diastolic dysfunction & Y axis represent The mean pulse pressure in patients with different grades of diastolic dysfunction. Mean pulse pressure gradually increased significantly towards grade III and IV diastolic dysfunction. (p=<0.001)=p value reached from one way ANOVA test, (Figure-18).

Patients were divided into two groups according to age (Above and below 50 yrs) Both age group has significant diastolic dysfunction in higher tertile of pulse pressure group. LV diastolic dysfunction in above and below 50 years of age group were 93% and 100%, in 3rd tertile pulse pressure with p value 0.01 and 0.05. Multiple regression analysis of some independent characteristics along with pulse pressure that may affect the diastolic function was done and pulse pressure was found most strongest independent predictor and p=<0.0001 (significant). Others predictors like Diabetes Mellitus had P value 0.01, Concentric LVH had P value 0.34 (not significant), Age had p value 0.59 (not significant). In 2023, total 90 patients were studied for strengthen the principal findings of our study (Pulse pressure and diastolic dysfunction). Baseline characteristics of this group were similar as previous study group. Diastolic dysfunction was seen in this group near similar pattern of previous group. Here we observed, in 1st tertile( n=32) were normal (28) 89%, diastolic dysfunction(4) 11% ; 2nd tertile (n=30) were normal(5) 16%, diastolic dysfunction (25) 84% ; 3rd tertile (n=28) were normal (2) 7%, diastolic dysfunction(26) 93%.

**Discussion**

During last decades several studies were done to find out the relationship between blood pressure and several cardiovascular risks. Several factors are responsible for high pulse pressure. It is frequently associated with changes in arterial elasticity particularly in patients with essential hypertension. Hypertensive patients develop early arterial stiffness and develop low diastolic with high systolic blood pressure. Previous study showed that it is a bad prognostic sign for cardiovascular mortality and morbidity.[14] Recently, concentration is given on Pulse pressure as a marker of several cardiovascular risks. The main results of the present study showed the significant association between pulse pressure (computing from resting blood pressure measurement) with the LV diastolic dysfunction in patients with essential hypertension.15 In this study, It was found that most of Hypertensive patient had pulse pressure above normal value and mean 48 mm of Hg. One study showed that the most of their study subjects pulse pressure were above the normal value & their mean pulse pressure was 52.5 mm of Hg.[15] So, our study patients pulse pressure were divided into three tertile group as like previous study.[12,15] Baseline demographic parameters of study patients were compared according to teriles of their pulse pressure that were not significantly differ from each other. But age of patients gradually increased significantly towards the higher tertile. Most important reason of it, the age of patients is another factor associated with modest increased of pulse pressure. Clinical parameters were not significantly differ from each other as shown in previous study.[15] Different echocardiographic parameters of left ventricular diastolic dysfunction were used in this study. Most of the parameters were significantly differ from each other that indicate the significant changes in LV diastolic function.[14,15] After analyzing the findings according to

tertiles of pulse pressure of study patients, LV diastolic dysfunction was found significantly more with increasing percentage, in 2nd (82% vs 18%) and highest (95% vs 5%) in third tertile of pulse pressure group(p <0.001). Previous study showed the Hypertensive patients those were in the highest tertile of PP had a significantly higher prevalence of concentric left ventricular hypertrophy and an initial impairment of diastolic function (23 vs 55%; P=<0.05). Another study showed similar result. In this study, proportion of diastolic dysfunction was found more in relation to previous other studies.[16] Possible reason of it that we had selected the patients who were not receiving any antihypertensive drugs or irregularly taking drugs and discontinued at the time of study. Nearly all patients in our study had uncontrolled hypertension. In this study, two age groups were defined, below and above 50 years.[16,17] Both age group showed significant association with wide pulse pressure and LV diastolic dysfunction. This study showed the highest tertile of pulse pressure group had significantly higher percentage concentric LVH and impairment of the diastolic function.(p<0.001). Concentric left ventricular hypertrophy (LVH) may be associated with LV diastolic dysfunction and common finding of systemic hypertension. This study divided the total patients into group according to presence or absence of LVH. Both group had shown significant diastolic dysfunction in highest tertile of pulse pressure group. Previous studies had shown the similar results.[17,18] So, Pulse pressure may have independent effect on LV diastolic dysfunction. In the present study logistic regression analysis revealed mean pulse pressure in different tertiles was strongest independent predictors of diastolic function (p<0.0001). For detection of diastolic function, most of the studies used only mitral inflow parameters but this study used several parameters including tissue Doppler parameters according to the ASE guideline (2008). In 2023, the presence of diastolic dysfunction gradually increased in higher tertile group which was almost similar to the findings of previous group (p value <0.05). So this study showed significant relationship between wide pulse pressure and Diastolic dysfunction in untreated hypertensive subjects. Our study differ from previous study regarding use of echocardiographic parameter that we have used several Doppler parameters, including tissue Doppler. Important observation of the present study was high detection of diastolic dysfunction and its significant association with wide pulse pressure. So pulse pressure may be considered an important clinical tool for detecting Cardiovascular morbidity in a hypertensive patient.

This study showed that hypertensive patients with a very wide pulse pressure likely to develop left ventricular diastolic dysfunction. Several factors are associated with the development of left ventricular diastolic dysfunction. Among them pulse pressure had strongest relation with left ventricular diastolic dysfunction. Early detection of left ventricular diastolic dysfunction will be possible by carefully observing the pulse pressure of the patient. During Follow up of the patient pulse pressure may be an important clinical marker to concentrate. Early detection of left ventricular diastolic dysfunction particularly in asymptomatic patients will help to reduce mortality and morbidity in hypertensive patients. This study had some limitations .So Large scale study needed to prove accurate relationship between pulse pressure and left ventricular diastolic dysfunction.

## Conclusion

Pulse pressure may used as an early clinical marker of left ventricular diastolic dysfunction in a patient with essential hypertension. early detection of LV diastolic dysfunction will be possible clinically & ultimately it will reduce mortality and morbidity.

**Conflict of interests:** None

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Original Article

# Significance of Estrogen Receptor (ER) Expression in Breast Carcinoma

Rina MNN


## Abstract

**Background:** Breast carcinoma is a major global health issue and a leading cause of cancer-related deaths. It originates from ductal or lobular cells, resulting in ductal or lobular carcinomas. Understanding the molecular mechanisms, particularly hormonal pathways, is crucial for developing targeted therapies. Estrogen receptor (ER) expression is a key factor in subtyping breast cancer and predicting responses to hormone therapies; approximately 75% of breast cancers are ER-positive.

**Aim of the study:** This study aims to explore the significance of ER expression in breast carcinoma, focusing on its role in predicting therapeutic outcomes, aiding in disease subtyping, and its potential as a prognostic marker.

**Methods:** This study collected breast cancer tumor tissues from patients who underwent surgery at Sylhet MAG Osmani Medical College between March 2019 and February 2021. Patient consent was secured, and the protocol was ethically approved. Among 72 patients, 52 were ER-positive, and 20 were ER-negative. Eligible patients had histologically confirmed breast cancer with no prior pre-operative therapies. Data on demographics, tumor histopathology, treatments, and survival were obtained from medical records, and follow-up checks were conducted every 6-12 months.

**Result:** Most patients in both groups were over 35 years old, with no significant age difference. ER-positive patients were more likely to be in stage T1 (53.85%) than ER-negative patients (35%) ($p < 0.05$) and had fewer high-grade tumors (17.31% vs. 60%). Progesterone receptor positivity was higher among ER-positive cases (82.69% vs. 5%, $p < 0.05$). Ki-67 levels were lower in ER-positive patients, with 71.15% below 10% ($p < 0.05$). Total mastectomy was the primary surgery, and endocrine therapy was significantly more commsson in ER-positive cases (90.38% vs. 10%).

**Conclusion:** This study underscores the importance of estrogen receptor (ER) expression in breast cancer, linking ER positivity to better prognostic features, lower tumor grade, and effective endocrine therapy response. ER-negative cancers, however, present higher grades and respond better to chemotherapy, highlighting ER's crucial role in personalized breast cancer treatment.


**Keywords:** ER expression and Breast carcinoma

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## Introduction

Breast carcinoma is a leading cause of cancer mortality worldwide and presents a significant public health concern.[1] The breast is composed of glandular, ductal, and connective tissues, which include two main structural components: ducts and lobules. These structures are lined by two epithelial cell types luminal and myoepithelial cells and surrounded by interlobular and intralobular stroma.[2] Breast cancer commonly arises from either the ductal or lobular cells, leading to ductal carcinomas or lobular carcinomas, respectively.[3] The incidence of breast cancer is highest in developed regions, such as Europe, Northern America, and Australia, and it is rising rapidly in developing countries, including Bangladesh.[4] Given its prevalence, understanding the molecular and biological mechanisms of breast cancer, especially the hormonal pathways involved, has become essential in developing targeted

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therapies and improving patient outcomes.[5,6,7] Estrogen receptor (ER) expression is one of the critical markers used to subtype breast carcinoma and predict responses to hormone-based therapies. Approximately 75% of breast cancers express ER, and these tumors generally respond well to endocrine therapies such as tamoxifen.[8] However, ER-negative tumors lack such responsiveness, underscoring the importance of precise molecular profiling in breast cancer management.[9,10] ER is a regulatory molecule that plays a key role in the growth of estrogen-responsive tissues, including the breast .11 The interaction between ER and estrogen not only stimulates proliferation but also increases the risk of genetic mishaps that can contribute to carcinogenesis.[7,12] Advances in immunohistochemistry techniques now allow for the accurate detection of ER in breast cancer tissues, including both invasive carcinomas and carcinoma in situ (CIS).[13,14] This has provided valuable insights into the biology of breast cancer and enabled better clinical management. The clinical significance of ER expression extends beyond simple classification. ER-positive tumors are associated with a more favorable prognosis and higher chances of treatment success with endocrine therapies.[1] However, the development of endocrine resistance in approximately one-third of patients highlights the need for additional biomarkers, such as cyclin D1, to enhance the accuracy of prognosis and guide future therapeutic strategies.[15] Cyclin D1, in particular, plays a dual role in cell cycle regulation and modulates ER activity through CDK-independent pathways, further influencing breast cancer behavior.[11] Recent research has identified various signaling pathways that interact with ER, contributing to breast cancer progression and therapy resistance. Understanding these interactions is crucial for developing comprehensive treatment strategies that improve patient outcomes. This study aims to explore the significance of ER expression in breast carcinoma, focusing on its role in predicting therapeutic outcomes, aiding in disease subtyping, and its potential as a prognostic marker.

**Methodology & materials**

We collected tumor tissue samples prospectively from breast cancer patients who had undergone surgical resection at the Department of Pathology, Sylhet MAG Osmani Medical College (SOMCH), Sylhet, Bangladesh, between March 2019 and February 2021. Informed written consent was obtained from patients or their guardians, and the study protocol was approved by the SOMCH Institutional Ethical Committee. Out of 72 patients, 52 were estrogen receptor (ER) positive, and 20 were ER-negative.

Inclusion Criteria:

- Female patients.
- Histologically confirmed cases of breast carcinoma, irrespective of patient age.

Exclusion Criteria:

- Breast cancer patients who received pre-operative radiotherapy, chemotherapy, or endocrine therapy.

Data Collection:

Patient demographics, tumor histopathology, treatment methods, and survival data were retrospectively obtained from medical records. Patients received either mastectomy or breast-conserving surgery combined with sentinel or axillary lymph node biopsies. Post-surgical care included radiotherapy or systemic adjuvant treatments as tolerated. Follow-up assessments were performed every 6-12 months, incorporating clinical exams, lab tests, and imaging to monitor for relapse. Tumor staging was assigned according to the American Joint Committee on Cancer's 6th edition criteria, and histological grading was evaluated using the modified Bloom-Richardson scale. Recurrence was defined as cancer reappearance at the initial or local site. In contrast, regional recurrence included spread to the ipsilateral axillary, supraclavicular, or internal mammary lymph nodes and distant metastasis encompassed recurrences at other remote sites.

Specimen Collection:

After patient admission, diagnosis was established through clinical examination and fine-needle aspiration cytology (FNAC). A trained surgeon performed mastectomies in the SOMCH Surgery Department. Specimens were preserved in 10% formalin, transported to the SOMCH Pathology Department for histopathological examination, and then stained with H&E to assess tumor type and grade. Immunostaining for cyclin D1 and ER was conducted at the Armed Forces Institute of Pathology.

Statistical Analysis:

Data were analyzed using SPSS version 27. Quantitative data were presented as mean and standard deviation, while qualitative data were shown as frequencies and percentages. All statistical tests were two-sided, and p-values <0.05 were deemed significant, utilizing Chi-square and Fisher exact tests where applicable.

**Result**

Among the total 72 participants of breast carcinoma, we found 52 cases of ER-positive, and the rest of the 20 cases were ER-negative (Figure-1). Table-I compares various clinical and pathological features between estrogen receptor (ER) positive and ER-negative breast cancer patients. The majority of patients in both groups were over 35 years old, with 94.23% of ER-positive and 90% of ER-negative patients being in this age range, showing no significant age difference. In terms of pathological T stage, a higher proportion of ER-positive patients were in stage T1 (53.85%) compared to ER-negative patients (35.00%), showing statistical significance ($p < 0.05$). Pathological N stage revealed that 53.85% of ER-positive patients and 65% of ER-negative patients had no nodal involvement (N0), which was also significant. Histological grading indicated a notable difference, with 82.69% of ER-positive patients in lower-grade tumors (I/II) versus only 40% among ER-negative patients. In contrast, 60% of ER-negative patients had high-grade (III) tumors, which was also significant. Among ER-positive cases (N=52), 82.69% were progesterone receptor-positive, while only 5% of ER-negative cases (N=20) were progesterone receptor-positive, showing statistical significance ($p<0.05$). For HER2 status, 21.15% of ER-positive patients were HER2-positive, compared to 35% of ER-negative patients, though this difference was not significant. Ki-67, an indicator of cell proliferation, showed significant variation, with 71.15% of ER-positive patients having Ki-67 levels under 10%, whereas 80% of ER-negative patients had Ki-67 levels of 10 or more ($p<0.05$) (Table-II). Table-III summarizes treatment approaches for breast cancer patients based on estrogen receptor (ER) expression. Among ER-positive patients (n=52), the majority (73.08%) underwent total mastectomy (TM), while 26.92% had breast-conserving surgery (BCS). Similarly, most ER-negative patients (n=20) also had TM (70%), with 30% opting for BCS, with no statistically significant difference. Radiotherapy was administered to 42.31% of ER-positive and 45% of ER-negative patients, with no significant variation. Chemotherapy was commonly used across both groups (82.69% ER-positive, 85% ER-negative), with significant differences. Endocrine therapy was notably higher in ER-positive patients (90.38%) than in ER-negative (10%), showing a significant difference.

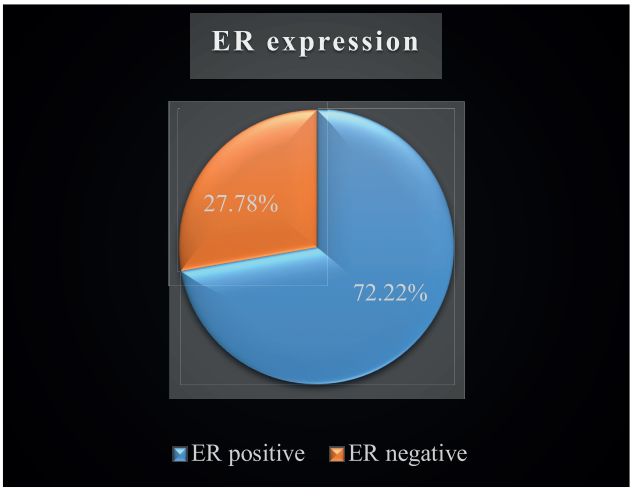



**Figure 1:** Prevalence of Estrogen Receptor (ER) Expression in the study participants (N=72).

**Table I:** Demographic and clinical features of study participants.

| Variables | ER positive (N=52) n | % | ER negative (N=20) n | % | P-value |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| ≤35 | 3 | 5.77 | 2 | 10.00 | ns |
| >35 | 49 | 94.23 | 18 | 90.00 | |
| Pathological T stage | | | | | |
| T1 | 28 | 53.85 | 7 | 35.00 | s |
| T2–4 | 24 | 46.15 | 13 | 65.00 | |
| Pathological N stage | | | | | |
| N0 | 28 | 53.85 | 13 | 65.00 | s |
| N1–3 | 24 | 46.15 | 7 | 35.00 | |
| Histological grade | | | | | |
| I/II | 43 | 82.69 | 8 | 40.00 | s |
| III | 9 | 17.31 | 12 | 60.00 | |

s: Significant, ns: Non-significant

**Table II:** Biological markers by ER expressions in study participants.

| Variables | ER positive (N=52) n | % | ER negative (N=20) n | % | P-value |
|---|---|---|---|---|---|
| Progesterone receptor | | | | | |
| Negative | 9 | 17.31 | 19 | 95.00 | s |
| Positive | 43 | 82.69 | 1 | 5.00 | |
| HER2 | | | | | |
| Negative | 41 | 78.85 | 13 | 65.00 | ns |
| Positive | 11 | 21.15 | 7 | 35.00 | |
| Ki-67 | | | | | |
| <10 | 37 | 71.15 | 4 | 20.00 | s |
| ≥10 | 15 | 28.85 | 16 | 80.00 | |

s: Significant, ns: Non-significant

**Table III:** Treatment details by ER expressions in study participants.

| Variables | ER positive (N=52) n | % | ER negative (N=20) n | % | P-value |
|---|---|---|---|---|---|
| Type of surgery | | | | | |
| BCS | 14 | 26.92 | 6 | 30.00 | s |
| TM | 38 | 73.08 | 14 | 70.00 | |
| Radiotherapy | | | | | |
| Not done | 30 | 57.69 | 11 | 55.00 | ns |
| Done | 22 | 42.31 | 9 | 45.00 | |
| Chemotherapy | | | | | |
| Not done | 9 | 17.31 | 3 | 15.00 | s |
| Done | 43 | 82.69 | 17 | 85.00 | |
| Endocrine therapy | | | | | |
| Not done | 5 | 9.62 | 18 | 90.00 | s |
| Done | 47 | 90.38 | 2 | 10.00 | |

s: Significant, ns: Non-significant

## Discussion

Breast cancer is a highly hormone-dependent malignancy, with estrogen and its receptor (ER) recognized as central players in both the development and progression of the disease. Estrogen receptor (ER) pathways are a primary target in breast cancer treatment, as blocking or modulating these pathways either directly or indirectly has shown significant efficacy in managing breast carcinoma.[16] ER signaling is vital in breast cancer carcinogenesis and influences disease phenotype and progression.[17] Traditionally, ER expression has been viewed as a binary characteristic either present or absent—allowing for straightforward patient stratification and therapeutic decision-making. However, recent findings suggest that a semi-quantitative approach to assessing ER could more accurately reflect treatment responsiveness. The current binary approach to ER expression is limited in that it may obscure the nuances of the therapeutic threshold required for optimal endocrine therapy (ET) outcomes.18 Research has demonstrated that tumors with ER positivity respond well to hormone therapies, with the extent of therapeutic benefit correlating closely to the level of ER expression within the tumor cells.[19,20] Conversely, tumors that lack ER expression (ER −) generally do not respond to hormonal treatments but may exhibit a stronger response to chemotherapy compared to their ER-positive (ER+) counterparts.[21] Androgens, while less emphasized than estrogens in breast cancer research, are also essential steroid hormones throughout a woman's life and serve as precursors in estrogen synthesis. Recently, the androgen receptor (AR) has gained recognition as a significant biomarker in breast cancer biology.[22,23] AR is detected in more than 60-70% of in situ and invasive breast cancers and often coexists with ER and progesterone receptor (PgR), though it is rarely co-expressed with HER2.[24,25] In our study, we observed a robust association between ER positivity and favorable clinicopathological characteristics, particularly among endocrine-responsive breast cancers, including non-triple-negative breast cancer (non-TNBC) subtypes. Notably, our findings indicated no significant interaction between ER and HER2 across the entire patient cohort, which aligns with previous research.[26,27] ER positivity emerged as a strong predictor of favorable prognostic markers. In patients with ER-positive tumors, better outcomes were consistently associated with this marker, which underscores its potential predictive value for systemic treatments, including endocrine therapies. Of the ER-positive subgroup in this study, 90.38% received either endocrine therapy or a combination of chemotherapy and endocrine therapy, reinforcing the relevance of ER expression in therapeutic strategy development. Studies further suggest an inhibitory interplay between ER and AR in vitro, with ER appearing to downregulate AR signaling in breast cancer cells.[28] Large retrospective analyses have identified AR as both a prognostic and predictive factor within ER-positive breast cancer cases, suggesting AR's potential utility as a biomarker to refine treatment plans within this subgroup.[26] ER-negative breast cancers, comprising approximately one-third of all cases, remain challenging as they derive limited benefit from endocrine

therapy and are often linked with poorer prognosis compared to ER-positive cancers.[16] This study demonstrated a high prevalence of ER-positive breast cancers (72.22%), reinforcing that ER positivity aligns closely with more favorable clinical and pathological outcomes in breast cancer patients. These findings underscore the significant impact of ER expression on prognosis and patient outcomes, highlighting the necessity of ER testing and consideration in breast cancer management. This study has several limitations. Only ER and cyclin D1 expressions were assessed, whereas other relevant biomarkers (e.g., androgen receptor or HER2) were not explored in detail. Future studies with larger cohorts and a broader range of biomarkers would provide more comprehensive insights into the role of ER expression in breast cancer prognosis and treatment responses.

## Conclusion

This study highlights the significant role of estrogen receptor (ER) expression in breast carcinoma, underscoring its value in prognostic stratification and therapeutic decision-making. ER-positive breast cancers are associated with more favorable clinicopathological characteristics and better responses to endocrine therapies compared to ER-negative cases. ER positivity correlates with lower tumor grade, reduced nodal involvement, and lower cell proliferation rates, making it a vital biomarker for predicting treatment outcomes and guiding systemic therapy choices. Conversely, ER-negative tumors generally show higher grades and a stronger response to chemotherapy but limited benefit from hormone therapies. These findings reinforce the clinical importance of ER testing in breast cancer, advocating for its routine use to enhance patient management and improve prognostic accuracy.

**Conflict of interests:** None

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Original Article

# Variations in the Origins of Thyroid Arteries in Bangladeshi People

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## Abstract

**Background:** Morphometry of the thyroid gland is clinically important in the evaluation and management of thyroid disorders. In some cases, where medical treatment is not sufficient to manage thyroid disorders, specially in malignancy and when there are compressive symptoms, e.g. pressure on trachea or esophagus causing dyspnoea or dysphagia, demand surgical intervention. The understanding of the anatomical relations, functional states and blood supply of the thyroid gland is of paramount importance to thyroid surgeons.

**Objectives:** This cross sectional type of descriptive study was conducted to determine the variations in the origin of thyroid arteries in Bangladeshi people.

**Methodology:** This was a cross sectional descriptive study. A total 60 cadaveric thyroid glands were studied in department of forensic medicine and toxicology, Rajshahi medical college from January, 2018 to January, 2019. The source of origin of superior thyroid artery, inferior thyroid artery and arteria thyroidea ima was also evaluated with fine dissection method.

**Results:** On both sides, the superior thyroid artery arose mostly from the external carotid artery (91.67%), while rests were found to be from the common carotid artery at its level of bifurcation (8.33%). The inferior thyroid arteries arose exclusively from the thyrocervical trunk on both sides in both males and females. 2 cases in right side and 3 cases in left side showed unilateral absence of the inferior thyroid artery. Presence of arteria thyroidea ima was not revealed in this study.

**Key words:** Superior thyroid artery, Inferior thyroid artery, Arteria thyroidea ema.

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## Introduction

The thyroid gland is the earliest endocrine gland to appear in mammalian development. It begins to form approximately 24 days after fertilization1. The thyroid gland is brownish-red in colour, highly vascular and placed anteriorly in the lower neck, level with the 5th cervical to 1st thoracic vertebrae. It has right and left lobes connected by a narrow median isthmus. Occasionally the isthmus is absent. The whole thyroid gland is ensheathed by pretracheal layer of deep cervical fascia[2]. The size and weight of thyroid gland vary with age, sex, physiologic state, race and geographical location.

The thyroid gland has a blood flow about 5 times the weight of the gland each minute, which is a blood supply as great as that of any area of the body with a possible exception of adrenal cortex[3]. The arteries supplying the thyroid gland are superior and inferior thyroid arteries and sometimes an arteria thyroidea ima. There is significant variation in the anatomy of these arteries, both among races and within individuals of same races4. Normally the superior thyroid artery takes its origin from the anterior surface of external carotid artery. The superior thyroid artery may issue from common carotid artery. But it may also arise frequently from the bifurcation of common carotid artery. Superior thyroid artery may occasionally be double, unilateral

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or completely absent. The inferior thyroid artery usually arises from thyrocervical trunk as a single trunk or as multiple branches. But it may also arise as a branch of subclavian artery[5]. Occasionally it may be absent[6].

Arteria thyroidea ima may be present in 1.5 to 12.2 percent of people. It may arise from the brachiocephalic artery, the right common carotid artery, the aortic arch or internal thoracic artery. The artery may be as large as inferior thyroid artery or a mere twig. Its frequent location anterior to trachea makes it of major importance during tracheostomy[7].

This postmortem study was proposed to observe the artery supply of the thyroid gland Bangladeshi cadavers which would give a guideline to the surgeons during thyroid surgery to prevent surgical complications.

**Materials and methods**

This cross sectional descriptive study was carried out in department of anatomy, Rajshahi medical college from January, 2018 to Januray, 2019. A total of 60 cadaveric thyroid glands were studied in department of forensic medicine and toxicology, Rajshahi medical college. Ethical clearance was taken prior to the study from the ethical review committee of Rajshahi medical college. Samples were collected within 24 hours of death before appearance of any sign of putrefaction. Unusual enlargement (e.g. goitre, carcinoma) and gross anomaly in architecture of the thyroid gland or any injury in the neck region (e.g. cut throat or hanging) were considered as ineligible cases for the study. The neck region was dissected to expose the thyroid gland by fine dissection method. During midline dissection of the neck in cadavers infrahyoid groups of muscles were displaced laterally. Sternothyroids and sternohyoids were cut near their lower ends and reflected upwards, thereby exposing pretracheal layer of deep fascia and fat. To note the source of origin of superior thyroid artery, the carotid triangle was exposed carefully. The upper part of the triangle was examined to observe its origin. Carotid sheath was disposed carefully with a tooth forceps.

To note the source of origin of inferior thyroid artery, the lower part of the neck was exposed carefully upto the upper border of clavicle and suprasternal notch. The first part of the subclavian artery was found out and searched for the branches of that part. The branches were traced to identify the inferior thyroid artery artery. The major branches of the arch of aorta was observed carefully in search of origin of arteria thyroidea ima.

**Results**

Total 60 cadaver were studied. 66.7% sample was male and 33.3% was female. Mean age was 36.68+12.23 years in male, 40.26+10.05 years in female and 37.82+11.62 years in total sample.

**Table-I:** Origin of the superior thyroid artery

| | | Source of origin | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Right | | | | Left | | | |
| Sex | Number | External carotid artery | | Common carotid artery | | External carotid artery | | Commonl carotid artery | |
| | | n | % | n | % | n | % | n | % |
| Male | 40 | 38 | 63.33 | 3 | 5.0 | 38 | 63.33 | 3 | 5.0 |
| Female | 20 | 17 | 28.33 | 2 | 3.33 | 17 | 28.33 | 2 | 3.33 |
| Total | 60 | 55 | 91.67 | 5 | 8.33 | 55 | 91.67 | 5 | 8.33 |

n= number

**Table-I:** showed the source of origin of the superior thyroid artery. The origin was studied in 60 cadavers. On both sides, the superior thyroid artery arose mostly from the external carotid artery (91.67%), while rests were found to be from the common carotid artery at its level of bifurcation (8.33%).

**Table-II:** Origin of the inferior thyroid artery

| Sex | Source of origin | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Right | | | | Left | | | |
| | Thyrocrvical trunk | | Subclavian artery | | Thyrocrvical trunk | | Subclavian artery | |
| | n | % | n | % | n | % | n | % |
| Male | 39 | 67.24 | 0 | 0 | 40 | 70.18 | 0 | 0 |
| Female | 19 | 32.76 | 0 | 0 | 17 | 29.82 | 0 | 0 |
| Total | 58 | 100.0 | 0 | 0 | 57 | 100.0 | 0 | 0 |

n= number

Table-II: showed the origin of inferior thyroid artery. The origin of inferior thyroid arteries was studied in 60 cadavers. The inferior thyroid arteries arose exclusively from the thyrocervical trunk on both sides in both males and females. 2 cases in right side (3.44%) and 3 cases in left side (5.20%) showed unilateral absence of the inferior thyroid artery. Fig 1-2 Show origin of the superior thyroid artyery from the external carotid artery and carotid bifurcation

Presence of arteria thyroidea ima was not revealed in this study.

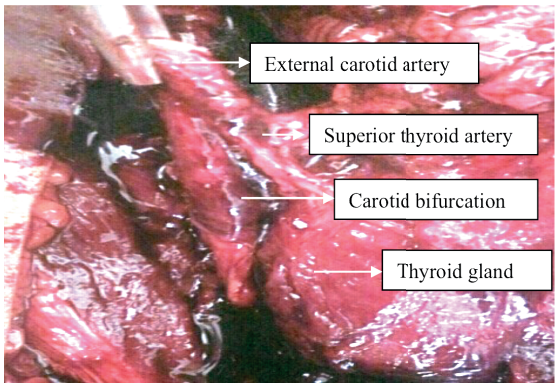



Fig-1: Showing origin of the superior thyroid artery from the external carotid artery.

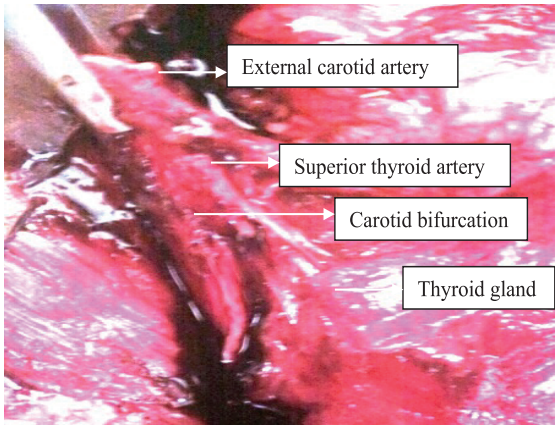



Fig-2: Showing origin of the superior thyroid artery from the carotid bifurcation.

**Discussion**

The present study was carried out on 60 human cadaver of different ages of both sexes (40 males and 20 females). The source of origin of superior thyroid artery, inferior thyroid artery and arteria thyroidea ima was also evaluated with fine dissection method.

In those cadavers, superior thyroid artery was most commonly originated from external carotid artery on both sides (55 out of 60 cadavers, 91.67%). Rest of cases showed an origin from the common carotid artery at the level of its bifurcation (5 out of 60 cadavers, 8.33%) (Table-I). None of the arteries showed origin from the trunk of common carotid artery. Those results were found to be correlated with the studies of Rimi KR et al. (2009) and Patel JP et al. (2013) where the origin of the superior thyroid artery was most commonly from external carotid artery[7,8]. Patel JP et al. (2013) found no origin of superior thyroid artery below the level of bifurcation. However, Rimi KR et al. (2009) showed origin of superior thyroid artery from common carotid artery below the level of bifurcation in few cases (17.5% in right side and 15.9% in left side).

The examination of inferior thyroid artery in the present study showed its origin exclusively from the thyrocervical trunk on both sides (Table-II). However, 2 cases in the right side (3.44%) and 3 cases in the left side (5.20%) showed the unilateral absence of the inferior thyroid artery. Rimi KR et al. (2009) showed the origin of inferior thyroid artery most commonly from the thyrocervical trunk, followed by subclavian artery. In that study, the inferior thyroid artery was absent in 9 cases out of 57 cadavers (3 in right and 6 in left). Graves MJ et al. (2018) established common carotid artery and vertebral artery as other sources of origin in some cases[9]. A study conducted by Rajamadhaba R et al. (2015) showed the similar result as the present study where the inferior thyroid artery originated from the thyrocervical trunk in all dissected cadavers10. In that study, left inferior thyroid artery was absent in a case. Esen K et al. (2018) conducted an study where right and left thyroid arteries were not identified in 2.2% and 7.0% of the individuals respectively[11].

In the present study, no dissected cadaver showed presence of arteria thyroidea ima. It was supported by a study conducted by Rajamadhaba R et al. (2015) where arteria thyroidea ima was absent from all cadavers10. Although Rimi KR et al. (2009) showed origin of arteria thyroidea ima in 10.52% cadavers7. In those cases it originated from brachiocephalic trunk, arch of aorta and common carotid artery.

**Conclusion**

Study of the thyroid arteries showed that, superior and inferior thyroid arteries were most commonly originated from external carotid artery and thyrocervical trunk respectively. Presence of arteria thyroidea ima was not revealed in this study.

Therefore, the present study will help to establish a reference of the variation of artery supply of thyroid gland in Bangladeshi people that may give guideline to the clinicians and surgeons, specially during thyroid surgery.

**Conflict of interests:** None

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Original Article

# Outcome of Guillain-Barré syndrome (GBS) Patients at Discharge with Conservative Management at a Tertiary Level Hospital

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## Abstract

**Background:** Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy marked by symmetrical muscle weakness and diminished or absent deep tendon reflexes.

**Objective:** To see the outcomes of Guillain-Barré Syndrome (GBS) patients at discharge with conservative treatment.

**Methods:** This prospective observational study was conducted in the Department of Neurology, Khulna Medical College Hospital, Khulna from January 2023 to December 2023 over a period of one year. A total of 30 GBS patients above the age of 18 were included. Patients having other underlying neurological conditions, as well as immunodeficiency disorders, were excluded. Functional outcomes were recorded on admission and discharge on the basis of Hughes disability score. All statistical analyses were performed by using SPSS software.

**Results:** Mean age of the patients was 32.94 ± 14.28 years. Males (93.3%) were predominant than females (6.7%). Male to female ratio was 17:1. On admission weakness was noted in both upper and lower limbs in 76.7% of cases, limited to upper limbs in 6.7%, and to lower limbs in 16.7%. Sensory symptoms included pain in 26.7%, paresthesia in 40.0%, numbness in 60.0%, and tingling in 30.0%. Dyspnea occurred in 20.0% of cases. Regarding preceding history, 60.0% had fever, 53.3% had diarrhea, 16.7% had vomiting and 20.0% had cough. Mean CSF protein was 81.53 ± 53.66 mg/dl, sugar 72.90 ± 26.76 gm/dl and cell count was 4.93 ± 0.83/cmm. Mean duration of treatment was 16.81 ± 3.76 days. At admission 13.3% patients had minor signs and symptoms, 16.7% were able to walk for 10 m or more without support, 23.3% were able to walk 10m with support, 30.0% were confined to bed and 16.7% required assisted ventilation. On discharge 6.7% were at healthy state, 20.0% patients had minor signs and symptoms, 23.3% were able to walk for 10 m or more without support, 23.3% were able to walk 10m with support, 16.7% were confined to bed and 16.7% required assisted ventilation. Hughes disability score significantly improved from 3.20 ± 1.29 (at admission) to 2.53 ± 1.43 (on discharge). Improvement in Hughes score on discharge was 0.66 ± 0.47.

**Conclusion:** The Hughes disability score for GBS exhibited a notable enhancement from 3.20 ± 1.29 at admission to 2.53 ± 1.43 at discharge. The enhancement in the Hughes score at discharge was 0.66 ± 0.47.

**Keywords:** Guillain barre syndrome, outcomes

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## Introduction

Guillain-Barré Syndrome (GBS) is an acquired autoimmune condition that impacts the peripheral nerve system, also known as post-infectious polyneuropathy or acute idiopathic polyneuritis. It may lead to respiratory or bulbar complications and manifests with various symptoms, including gait abnormalities, pain, weakness, rapidly ascending symmetric flaccid paralysis, areflexia, sensory disturbances, and differing levels of autonomic involvement. cerebral fluid protein levels without pleocytosis.[1] Furthermore, GBS is distinguished by increased It impacts roughly 1.1 individuals per 100,000 globally each year.[2]

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Although GBS can manifest in individuals of any age, its prevalence escalates with advancing age, and it exhibits a notable male predominance, particularly for an immunological disorder.[3]

It is now commonly acknowledged that GBS is caused by a T-cell autoimmune pathogenesis, which is frequently brought on by earlier events, especially viral or bacterial infections.[4] According to Susuki et al., there is the strongest correlation between the axonal-motor type of GBS and Campylobacter jejuni infection.[5] Hughes et al. have identified CMV, EBV, hepatitis B, and mycoplasma pneumonia as other related illnesses.[6]

GBS incidence, demographics, clinical features, diagnostic techniques, treatment modalities, and prognosis vary significantly by geography.[7-10] These discrepancies are due to a variety of variables. The regional presence of infectious agents such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Campylobacter influences GBS incidence rates.[11] Furthermore, hygiene habits influence pathogen exposure, which may impact GBS development.[12] Dietary behaviours and dietary inadequacies also influence disease progression.[13] GBS can be caused by specific environmental conditions,[14] whereas genetic differences between populations influence susceptibility and severity.[14,15] Underdiagnosis or misdiagnosis in areas with limited diagnostic resources can distort incidence numbers.[12] Variations in diagnosis criteria and reporting techniques hinder estimating GBS burden.[7,12] The lack of economical and effective therapies exacerbates outcomes in low- and middle-income countries, where socioeconomic issues such as poverty and inadequate healthcare infrastructure limit access to timely care.[12] The majority of extensive studies on GBS come from high-income regions, mainly North America and Europe, emphasizing the importance of current data from low- and middle-income countries.

Variable outcomes of GBS have been documented in Bangladesh[16], Thailand[17], India[18], China[19] and several other Asian nations.[20] Prognosis differs by area and clinical subtypes; axonal GBS generally has worse outcomes, especially in patients presenting with severe weakness who necessitate breathing assistanc[e.19,2]1 The proportion of GBS patients requiring assisted breathing during hospitalisation varies from 19% to 43% across several studies. Mechanical ventilation (MV) and admissions to the intensive care unit (ICU) entail risks of complications such as pneumonia, urinary tract infections, sepsis, electrolyte imbalances, pneumothorax, deep vein thrombosis, and cardiac ischaemia. Notwithstanding improvements in ICU management, mechanical ventilation and its associated problems are correlated with poorer outcomes.[22,23] This study was meant to evaluate the short-term consequences of GBS.

**Methods**

This prospective observational study was conducted in the Department of Neurology, Khulna Medical College Hospital, Khulna from January 2023 to December 2023 over a period of one year. A total of 30 diagnosed GBS patients (presented within 2 weeks of the onset of symptoms) age above 18 years who admitted during the study period were enrolled in this study. GBS was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) criteria .30 Patients with severe allergic reaction to correctly matched blood products, known selective IgA deficiency, HIV reactive and hypokalemia, previous steroid therapy, severe concurrent disease and pregnant women were excluded. Demographic, clinical, general examination, motor function, serum electrolyte, CSF data and duration of treatment were recorded. Statistical analysis was performed using SPSS software. Continuous data were presented as mean with standard deviation. Categorical data were presented as frequency with percentage. According to the Hughes Scale on admission and discharge, all the patients were graded to obtain the functional outcomes.

**Guillain Barré Syndrome disability scale, adapted from Hughes et al.24**

| Score | Clinical examination |
|---|---|
| 0 | A healthy state |
| 1 | Minor signs and symptoms |
| 2 | Able to walk for 10m or more without support |
| 3 | Able to walk 10m with support |
| 4 | Confined to bed |
| 5 | Required assisted ventilation |
| 6 | Death |

**Results**

**Table I:** Demographic profile of the study subjects (N=30)

| | Frequency (n) | Percentage (%) |
|---|---|---|
| Age (years) | | |
| ≤30 | 18 | 60.0 |
| >30 | 12 | 40.0 |
| Mean ± SD | 32.94 ± 14.28 | |
| Gender | | |
| Male | 28 | 93.3 |
| Female | 2 | 6.7 |

Maximum patients were in age ≤30 years (60.0%). Mean age of the patients was 32.94 ± 14.28 years. Males (93.3%) were predominant than females (6.7%). Male to female ratio was 17:1.

**Table II:** Clinical features of the study subjects (N=30)

| Symptoms | Frequency (n) | Percentage (%) |
|---|---|---|
| Weakness of all limbs | | |
| Both upper and lower limbs | 23 | 76.7 |
| Upper limbs | 2 | 6.7 |
| Lower limbs | 5 | 16.7 |
| Sensory symptom | | |
| Pain | 8 | 26.7 |
| Paresthesia | 12 | 40.0 |
| Numbness | 18 | 60.0 |
| Tingling | 9 | 30.0 |
| Dyspnea | 6 | 20.0 |

Weakness was observed in both upper and lower limbs in 76.7% cases, only in upper limbs (6.7%) and only in lower limbs (16.7%). Regarding sensory symptom, pain was observed in 26.7% cases, paresthesia in 40.0% cases, numbness in 60.0% cases, Tingling in 30.0% cases. Dyspnea was present in 20.0% cases.

**Table III:** Preceding history of the study subjects (N=30)

| | Frequency (n) | Percentage (%) |
|---|---|---|
| Fever | 18 | 60.0 |
| Diarrhea | 16 | 53.3 |
| Vomiting | 5 | 16.7 |
| Cough | 6 | 20.0 |

Regarding preceding history, 60.0% had fever, 53.3% had diarrhea, 16.7% had vomiting and 20.0% had cough.

**Table IV:** General examination of the study subjects (N=30)

| General examination | Mean ± SD | Min - max |
|---|---|---|
| R/R (breaths/min) | 19.33 ± 3.87 | 14 - 27 |
| Pulse (beats/min) | 78.80 ± 7.70 | 70 - 100 |
| Systolic BP (mmHg) | 118.33 ± 10.53 | 90 - 140 |
| Diastolic BP (mmHg) | 78.33 ± 8.74 | 60 - 110 |

Mean respiratory rate was 19.33 ± 3.87 breaths/min, pulse was 78.80 ± 7.70 beats/min, systolic BP was 118.33 ± 10.53 mmHg and diastolic BP was 78.33 ± 8.74 mmHg.

**Table V:** Sensory signs of the study subjects (N=30)

| | Frequency (n) | Percentage (%) |
|---|---|---|
| Intact | 30 | 100.0 |

Sensory signs were found intact in all cases.

**Table VI:** Serum electrolyte of the study subjects (N=30)

| | Mean ± SD | Min - max |
|---|---|---|
| Na+ (mEq/L) | 135.44 ± 3.52 | 128.60 - 141.40 |
| K+ (mEq/L) | 4.07 ± 0.31 | 3.46 - 4.85 |
| $Cl^-$ (mEq/L) | 100.46 ± 4.09 | 94.00 - 107.00 |

Mean Na+ was 135.44 ± 3.52 mEq/L, K+ was 4.07 ± 0.31 mEq/L and Cl- was 100.46 ± 4.09 mEq/L.

**Table VII:** CSF (cerebrospinal fluid) findings (N=30)

| | Mean ± SD | Min - max |
|---|---|---|
| Protein (mg/dl) | 81.53 ± 53.66 | 15.00 - 210.00 |
| Sugar (gm/dl) | 72.90 ± 26.76 | 45.04 – 153.14 |
| Cell count (/cmm) | 4.93 ± 0.83 | 4.00 - 6.00 |

Mean CSF protein was 81.53 ± 53.66 mg/dl, sugar 72.90 ± 26.76 gm/dl and cell count was 4.93 ± 0.83/cmm.

**Table VIII:** Hughes score on admission and discharge (N=30)

| Hughes disability score | On admission n (%) | On discharge n (%) |
|---|---|---|
| 0 | 0 | 2 (6.7) |
| 1 | 4 (13.3) | 6 (20.0) |
| 2 | 5 (16.7) | 7 (23.3) |
| 3 | 7 (23.3) | 7 (23.3) |
| 4 | 9 (30.0) | 5 (16.7) |
| 5 | 5 (16.7) | 3 (10.0) |
| Mean ± SD | 3.20 ± 1.29 | 2.53 ± 1.43 |

At admission, 13.3% patients had minor signs and symptoms, 16.7% were able to walk for 10 m or more without support, 23.3% were able to walk 10m with support, 30.0% were confined to bed and 16.7% required assisted ventilation. At discharge, 6.7% were at healthy state, 20.0% patients had minor signs and symptoms, 23.3% were able

to walk for 10 m or more without support, 23.3% were able to walk 10m with support, 16.7% were confined to bed and 16.7% required assisted ventilation. Hughes disability score significantly improved from 3.20 ± 1.29 (at admission) to 2.53 ± 1.43 (on discharge) (Table VIII). Improvement in Hughes score on discharge was 0.66 ± 0.47. Mean duration of treatment was 16.81 ± 3.76 days.

**Discussion**

Maximum patients were in age ≤30 years (60.0%). Mean age of the patients was 32.94 ± 14.28 years. In the study of Velásquez-Rimachi et al.25, age was <65 years in 87.0% patients. Maximum patients were <35 years (76.7%) in the study of Tewedaj et al.26 Mean age was 48.28 years.27 A higher incidence in males is noted throughout the literature, with previous studies reporting a relative risk of 1.78 (Sejvar et al., 2011).28 Males (93.3%) were predominant than females (6.7%). Male to female ratio was 17:1. Similar to this study male was predominant (70.7%) in the study of Velásquez-Rimachi et al.25 and Siddiqui et al.27.

In this study, weakness was observed in both upper and lower limbs in 76.7% cases, only in upper limbs (6.7%) and only in lower limbs (16.7%). Regarding sensory symptom, pain was observed in 26.7% cases, paresthesia in 40.0% cases, numbness in 60.0% cases, Tingling in 30.0% cases. Dyspnea was present in 20.0% cases. Quadriparesis was observed 81.1% of the GBS patients in the study of Velásquez-Rimachi et al.25

Regarding preceding history, 60.0% had fever, 53.3% had diarrhea, 16.7% had vomiting and 20.0% had cough in this study. In the study of Velásquez-Rimachi et al.25, gastrointestinal infection was 30.4% and respiratory infection was 19.6%. History of preceding infection was 49.1% case who did not require MV.27

Baseline mean respiratory rate was 19.33 ± 3.87 breaths/min, pulse was 78.80 ± 7.70 beats/min, systolic BP was 118.33 ± 10.53 mmHg and diastolic BP was 78.33 ± 8.74 mmHg in this study. Pulse was 96 ± 17 meats/min, systolic BP was 113 ± 16 mmHg and diastolic BP was 74 ± 12 mmHg at admission in the study of Bhagat et al.29

Mean Na+ was 135.44 ± 3.52 mEq/L, K+ was 4.07 ± 0.31 mEq/L and Cl- was 100.46 ± 4.09 mEq/L.

In this study, mean CSF protein was 81.53 ± 53.66 mg/dl, sugar 72.90 ± 26.76 gm/dl and cell count was 4.93 ± 0.83/cmm. Normal CSF protein was found in one-third to one-half of patients within the first week after symptom onset. The presence of albuminocytologic dissociation increases to more than 75 per cent of patients in the third week after symptom onset.4 It is therefore recommended that CSF samples should be collected at least two weeks after symptom onset in order to be used to support a diagnosis of GBS. Mean duration of treatment was 16.81 ± 3.76 days in this study. The median length of hospitalization was 14 days.25

At admission, 13.3% of patients exhibited minor signs and symptoms; 16.7% could walk 10 meters or more without support; 23.3% could walk 10 meters with support; 30.0% were bedbound; and 16.7% required assisted ventilation. By discharge, 6.7% were at healthy state, 20.0% patients had minor signs and symptoms, 23.3% were able to walk for 10 m or more without support, 23.3% were able to walk 10m with support, 16.7% were confined to bed and 16.7% required assisted ventilation. The Hughes disability score improved significantly from 3.20 ± 1.29 at admission to 2.53 ± 1.43 at discharge, reflecting an improvement of 0.66 ± 0.47. In the study of Patel et al.30, on admission 4.0% had minor signs and symptoms; 16.0% could walk 10 meters or more without support; 22% could walk 10 meters with support; 38.0% were bedbound; and 10.0% required assisted ventilation. While at discharge, 6.0% had minor signs and symptoms; 26.0% could walk 10 meters without support, 28.0%could walk 10 meters with support, 38.0% were bedbound, and 2.0% were dead. The Hughes disability score improved significantly from 3.56 ± 1.14 at admission to 3.0 ± 0.95 at discharge,

**Conclusion**

According to the Hughes disability score, GBS significantly improved from 3.20 ± 1.29 at admission to 2.53 ± 1.43 at discharge with conservative management(respiratory support, cardiac monitoring, nutritional support, infection prevention, managing immobility-related complications, bowel and bladder management, rehabilitation). The improvement in the Hughes score upon discharge was 0.66 ± 0.47.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Case Report

# Cardiac Tamponade as First Presentation in Hypothyroidism: A case Report

Kamruzzaman M[1], Ghosh B[2], Jahan L[3]

## Abstract

Hypothyroidism is an endocrine disorder with multiorgan involvement and various complications. One of the significant but less often seen complications is pericardial effusion. Since it can progress to life-threatening conditions like cardiac tamponade and hemodynamic instability. Early diagnosis and management of the pericardial effusion in hypothyroidism is a must. We present a case of a 45-year-old male who presented with Shortness of breath for 2 months, Swelling of the face and legs for 3 months with cold intolerance, loss of appetite, constipation, daytime somnolence, fatigue, and hoarseness of voice for same duration. Laboratory investigation showed high thyroid-stimulating hormone (TSH), low triiodothyronine (T3), and raised serum anti-thyroid peroxidase (anti-TPO). The lipid profile demonstrated hyperlipidemia. Ultrasonography of the neck revealed normal thyroid size with decreased echo texture and increased vascularity. An electrocardiogram showed low voltage complexes with sinus bradycardia. 2D echocardiography revealed features of cardiac tamponade with normal ventricular function, In CCU Pericardiocentesis of 500 ml straw colored fluid was done & The patient was managed with thyroxine therapy which gradually resolved his symptoms and pericardial effusion. Pericardial effusion in hypothyroidism is due to the increased capillary permeability and albumin distribution volume and reduced lymph drainage in the pericardial cavity. Its presence in mild cases of hypothyroidism is uncommon although it can be seen in severe, long-standing hypothyroidism. Pericardial effusion in hypothyroidism, though rare, can present in mild cases and if overlooked can be fatal due to conditions like cardiac tamponade. With early cardiac assessment and intervention & adequate thyroid replacement therapy, pericardial effusion with temponade in hypothyroidism can be reversible lifesaving. But specialized hospital care is necessary. So, pericardial effusion which can be overlooked in many cases of hypothyroidism needs to be identified and managed early.

Keywords: Shortness of breath, Generalized swelling, Hypothyroidism, Cardiac Tamponade

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## Introduction

Hypothyroidism is a prevalent endocrine disorder with a wide range of symptoms and multiorgan involvement[1]. Among its numerous complications, pericardial effusion is a notable complication[2]. Pericardial effusion can occur in severe and long-standing hypothyroidism although it is uncommon it may cause massive pericardial effusion even temponade in unteated cases and can rarely present even as the primary presentation of hypothyroidism[3,4].

Here in we report a case of a 45-year-old male with hypothyroidism and cardiac tamponade as first presentation. This study shows that untreated, long standing hypothyroid case may cause massive pericardial effusion and although very rare but may lead to temponade. Early cardiac assessment with intervention and adequate thyroid replacement therapy, pericardial temponade & effusion in hypothyroidism can be reversed.

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**Case presentation**

Mr. X, 45 year old male, normotensive, non-diabetic, hailing from Demra, Dhaka presented with shortness of breath for last 2 months which was insidious onset and gradually progressive, initially during strenuous activities and for the last two weeks on mild exertion. But for the last two days it was so severe that he become breathless even at rest with NYHA class IV status and diagnosed as a case of severe pericardial effusion with features temponade in CCU of NICVD on 29.01.25, Pericardiocentesis of 500 ml straw colored fluid was done. The shortness of breath was not associated with cough, fever, chest pain, hemoptysis, redness of legs, unconsciousness. It had no seasonal or diurnal variation, not aggravated by dust, fumes or cold exposure. He denied history of Paroxysmal nocturnal dyspnea & Orthopnea. The patient also gave history of generalized swelling for the last 3 months. It was insidious in onset, first noticed as periorbital puffiness then progressively involved all over the body. It was associated with loss of appetite, cold intolerance, constipation, hoarseness in voice, daytime somnolence, malaise, lethargy, fatigue, body ache but not associated with headache, seizure, vomiting or blurring of vision, tingling, numbness in hand and feet.

However, there was no history of abdominal swelling, shortness of breath, chest pain, palpitation, reduced urine output, or passing frothy or blood in the urine. His bowel and bladder habits were normal. There was no drug history, no history of similar illness in the past, or on any other family members but he had previous history of orthopedic surgery in right leg due to Road traffic accident 3 years back and had been suffering from chronic osteomyelitis. Later due to his present complaints he was referred to NICVD, Dhaka for further evaluation & management. In NICVD CCU, quick clinical assessment and echocardiography was done and diagnosed as a case of pericardial temponade. On examination before pericardiocentesis, along with dyspnea and puffy face there was raised JVP, low BP 80/50 mm of Hg, soft heart sound, clear lung base, pulsus paradoxus, low voltage ECG, normal cardiac enzymes. Echocardiography was done by cardiologist in CCU revealed severe pericardial effusion with diastolic with clear indentation in RV during diastole, IVC dilated and show minimum variation during respiration with normal LV Ejection fraction. His thyroid status was not seen previously. Emergency pericardiocentesis was done there and approximately 500 ml straw colored fluid was aspirated from front of his chest.

On examination after pericardiocentesis, he was ill looking with periorbital swelling, loss of lateral eyebrows, hoarseness of voice, dry sparse thin hair, coarse skin. There was thickened and blackish discoloration of right lower leg with multiple sinus tracts with pus point.

He was mildly anemic and there was pitting edema. His vitals were normal. JVP was not raised and thyriod gland was not enlarged. Precordial examination revealed apex beat not palpable with less audible heart sounds. There was delayed relaxation of ankle jerk. Other systemic examinations was normal.

• On laboratory investigation, complete blood count (CBC), renal function test (RFT), liver function test (LFT), along total serum protein and albumin were normal. The patient underwent a thyroid function test which revealed high thyroid-stimulating hormone (TSH) 255.64 $\mu$IU/ml (0.4–6.1) and low triiodothyronine (T3) & tetraiodothyronine(T4). Ultrasonography (USG) of the neck showed normal thyroid size but decreased echo (CXR P/A view showing heart is enlarged in transverse diameter) 12 lead surface ECG Shows Rate- approx. 65 bpm

• Rhythm- Regular
• QRS- Normal
• Low voltage ECG

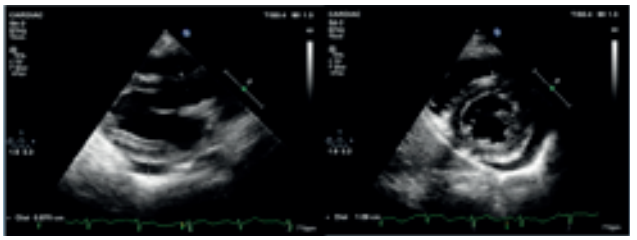


Fig. 1. 2D echocardiographic findings demonstrating severe pericardial effusion after at presentation.

texture and increased vascularity. Serum anti-TPO antibodies were high of 1412.9 (Negative if < 340/ml). The lipid profile demonstrated hypertriglyceridemia of 435 mg/dl. His serum Vitamin D, calcium, and phosphorus level were within the normal range. Electrocardiogram (ECG) revealed low voltage complexes with sinus bradycardia.

2D echocardiography, when done by a cardiologist, revealed features of severe pericardial effussion with normal ventricular function (Fig. 1) Pericardial Fluid Study reveals Glucose 84 mg/dl, LDH 303 U/l, Protein 65gm/l, ADA 19 U/l, AFB & Gm Staining , Gene XPERT reveals no microorganism found.

He was admitted to the CCU ,after pericardiocentesis 500 ml straw colour fluid drawn & sent for pericardial fluid study and later on managed with tablet Thyroxine 200 mg OD for two days and continued with 100 mg OD along with anti- lipid drug, tablet Fenofibrate 160mg PO OD at night. The patient was symptomatically better after a few days of treatment. The pedal edema gradually subsided, and the hoarseness of voice improved after one week of thyroxin therapy. TSH was repeated after two months of thyroxin therapy and was within the normal limit. He was not symptomatic later, generalized swelling subsided, and 2D echocardiography was normal after 2 months of therapy. Presently the patient is taking tab thyroxine 100mg OD and is on regular follow-up.

**Discussion**

Hypothyroidism is a prevalent endocrine disease worldwide. It can be asymptomatic or present with a wide range of non-specific symptoms that can delay the diagnosis even when the diagnosis is straightforward with simple laboratory tests[1]. More so with its complications, which can be life-threatening if not diagnosed and managed in time[3].

Cardiac tamponade is one of the significant rare complications in hypothyroidism. The incidence of pericardial effusion varies to be as high as 80% in severe, long- standing, and congenital hypothyroidism, and only 3% in early stages and mild form of the disease[6]. The frequency of pericardial effusion in well-established myxedema justifies the need to assess pericardial effusion; however, its occurrence in mild cases and as first presentations cannot be overlooked[4,7].



Fig. 2. Features of Hypothyroidism.

Among the several known etiologies of pericardial effusion, including malignancy, infection (TB), heart failure, radiation, trauma, connective tissue disorder, iatrogenic cause and metabolic causes, idiopathic pericarditis, usually of viral origin, remains the common cause of pericardial effusion, whereas metabolic disorder like hypothyroidism is considered unusual[8,9].




Fig-3: Chest X-ray P/A View

The pericardial effusion in hypothyroidism is attributed to the increased capillary permeability and albumin distribution volume and reduced lymph drainage in the pericardial cavity[1,8]. The effusion develops over time due to the accumulation of considerable volume usually without causing cardiac tamponade and alarming symptoms[1,3]. Thus, the absence of clinical symptoms may underestimate the total volume of effusion and disease severity.

But in rare occasion & neglected situation patient may present with cardiac temponade.

Patients with hypothyroidism tend to have pericardial effusion detected by echocardiography up to 30%[9,10]. Cardiomegaly on chest X-ray can have up to 38% false-positive rate and up to 30% false-negative rate, as demonstrated by Kerber et al. for pericardial effusion[11], while neither Kerber et al. nor Hardisty advised low voltage ECG readings to be specific for pericardial effusion [10,11]. Low voltage QRS complex can occur in hypothyroidism due to multiple reasons, notably advancing patient age, thyroid hormone deficiency itself but usually severe or pericardial effusion[12]. Cardiac temponade has some special features like dyspnea on minimal exertion or rest,



Fig. 4. ECG

low BP, raised JVP, soft heart sound, pulsus paradoxus. Echocardiographic features are presence pericardial effusion, diastolic RV collapse, systolic collapse of RA, Minimal respiratory variation of IVC diameter.[12]

Owing to potential complications related to hypothyroidism, identification and subsequent management are required at an early stage. However, due to infrequent association among them, further exploration and experimentation are required to develop optimum care[13]. Just as other symptoms of hypothyroidism, pericardial effusions can be reversed over time with thyroid hormone replacement[14]. Thus, it is important to assess thyroid function in cases of pericardial effusion and vice versa. Also, early assessment and management of pericardial effusion in hypothyroidism are vital to protect patients from life-threatening conditions like cardiac tamponade and hemodynamic instability[13].

## Conclusion

Hypothyroidism is one of the uncommon etiology causing massive pericardial effusion. Even though it occurs in long-standing myxedema, it can occur in mild cases too, which when unnoticed can be fatal like pericardial temponade. Since with early cardiac assessment and emergency intervention, adequate thyroid replacement therapy, the pericardial effusion and pericardial temponade due to hypothyroidism can be reversible, so it needs to be identified and managed early.

**Conflicts of interest:** None

Declaration of competing interest

## Acknowledgement

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