ISN: 199-7124 (Print)
NLM ID: 101184601
www.bmcjournal.com

# Bangladesh Medical College Journal

Vol. 23 January 2018 No. 1

# Contents

# BANGLADESH MEDICAL COLLEGE JOURNAL

**Vol. 23 No. 1 January 2018**

Official Publication of Bangladesh Medical College
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# Bangladesh Medical College Journal

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# Editorial

# Chikungunya Outbreak 2017 in Bangladesh: A Lesson for Sustainable Community Preparedness

Begum R

In Bangladesh, the first chikungunya outbreak was identified in Rajshahi and Chapainawabganj districts in 2008 with 39 cases.[1] Thereafter, serologic evidence has confirmed occurrence of outbreaks and sporadic cases from Dhaka and some rural areas.[2,3] In October 2011, an outbreak of fever consistent with Chikungunya occurred in Dohar of Dhaka District.[4] In 2014, six confirmed cases of CHIKV were reported from Dhaka, recently swayed with a severe outbreak of chikungunya with 2,314 cases from May to September 2017[5] and also Kabir et al reported that more than 18 million people were affected in the capital city of Bangladesh up to September 2017.[6]

The word Chikungunya is a Makonde word referring to the posture of bending that the affected patient acquires. Chikungunya virus is a mosquito-borne virus of the Togaviridae family which is small, spherical, enveloped, positive-strand RNA genome, about 60-70 nm diameter capsid.[7] Chikungunya fever is transmitted by Aedes aegypti and Aedes albopictus. Aedes aegypti breeds in stored fresh water in urban and semi-urban environments.[8] In 1952 Chikungunya fever was first reported from Makonde plateaus, along the borders between Tanzania and Mozambique.[9] Ross first isolated Chikungunya virus in 1953 from the serum of a febrile human during an epidemic in Newala district of Tanzania.[10] Chikungunya virus has become a more global concern and was listed as a priority by the Scientific Leadership Group for the Global Virus Network.[11] Probably Chikungunya virus was originated in Africa[12] and could be maintained in 'sylvatic cycle' involving wild primates and forest dwelling mosquitoes.[13] In Asia Chikungunya virus was introduced subsequently where it has been transmitted from human to human mainly by Aedes aegypti and, to a lesser extent by Aedes albopictus through an urban and semi-urban transmission cycle.[14] Since then Chikungunya has been reported in Burma, Thailand, Cambodia, Vietnam, India, Sri Lanka, Indonesia, West Africa and the Philippines.[15] In India, first outbreak occurred in Kolkata in 1963, since then a number of outbreaks occurred in Maharashtra, Andhra Pradesh, Tamil Nadu, and Barsi from 1964 to 1973. The virus re-emerged in 2006 and spread in 13 Indian states. About 2994 individuals out of a total 60,777 suspected chikungunya cases lost their lives.[16] In 2010, the National Capital Region of India was the seroprevalence rate 9.91%.[17] In 2016, Mumbai reported 12.5% seroprevalence rate.[18]

CHIKV from the 2017 outbreak in Dhaka was found to be genetically distinct from the strain Bangladesh/0810aTw, lacking A226V substitution. The Dhaka outbreak strains constitute a new cluster within the Indian Ocean clade, associated with E1 sequence diversity, suggesting that they are novel variants within the ECSA genotype. Further genetic and epidemiologic studies are necessary in Bangladesh to monitor the spread of the variant CHIKV and to define molecular characteristics relevant to large outbreaks in Dhaka.[19]

In recent years there have been explosive outbreaks of chikungunya fever in several parts of the SEA (South East Asia) Region and elsewhere. Although the disease is self-limiting, morbidity can be very high in major outbreaks resulting in a heavy social and economic toll. The disease should be preventable and it would require a planned approach, besides knowledge and awareness of early warning signs, for prevention.[20] Adult mosquito control measures such as fogging often applied by the civic authorities as a single tool may not by itself contribute to the effective containment of an outbreak. So integrated vector management through the elimination of breeding sites, use of anti-adult and anti-larval measures and personal protection will contribute to preventing an outbreak.

Community empowerment and mobilization is crucial for prevention and control of chikungunya. In 2017, DGHS in Bangladesh Health took the key role in creating awareness among the mass population and adopted a week long programs all over the Bangladesh including the medical colleges and all other health organization. Hopefully as consequence of those initiatives in 2018 we shall not have to face an epidemic of chikungunya disease. Now we need to motivate people prior to the seasonal outbreak and sustain the initiatives at individual, family, community and national level. Non-govt. organizations, private organizations and other stake holders may also campaign to combat the challenge collectively.

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# Original Article

# Sarcomatoid Carcinoma of Pancreas in Pancreatic Stone Disease- A Rare but Aggressive Malignancy with Gloomy Outcome

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## Abstract

**Background:** Chronic pancreatitis is a disease of remission and relapse. Pancreatolithiasis, when presents with mass lesion results into diagnostic dilemma and therapeutic uncertainty. Although these are commonly chronic inflammatory fibrotic lesions but 4% cases were associated with malignancy. When these mass lesions are Sarcomatoid carcinoma, the outcome is gloomy. Sarcomatoid carcinoma (SC) or Carcinosarcoma (CS), rarely occurs in pancreas. For all kind of pancreatic tumors, Resection is the gold standard treatment.

**Objective:** The objective of the study was to evaluate the clinical profile of Sarcomatoid carcinoma of pancreas in patients with pancreatic stone disease presenting with mass lesion and also to assess and correlate the mode of presentation, staging of the disease and outcome after surgery.

**Methods:** Total 12 patients were included in this study who were operated between June 2000 to January 2017 (17 years) and followed up to maximum 22 months. All were diagnosed cases of pancreatic stone disease. Age distribution, sex, clinical presentations, tumor location, stage of the disease and survival were documented in this study.

**Results:** Male patients were 58.3%. Maximum patients (41.6%) were in age group of 40-49 years. All patients presented with abdominal pain, vomiting and weight loss and 83.3% with steatorrhoea. About 50% tumor were located at head and body of pancreas, 50% of the patients were locally advanced and 41.6 % were with metastatic disease. Cases with curative resections and palliative surgeries revealed better survival with improved quality of life. However, with metastatic disease only 6 patients survived for 5 to 9 months.

**Conclusions:** Sarcomatoid carcinoma of pancreas is a rare aggressive malignancy. High index of suspicion is essential for early diagnosis. Pancreatic resection in early stage of malignancy gives hope of cure. Delayed presentation was the main obstacle for curative surgical resection.

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**Keywords:** Sarcomatoid carcinoma, Pancreatic stone disease, distal pancreatectomy, Anaplastic carcinoma

**Abbreviations:** SC= Sarcomatoid Carcinoma, CS= Carcinosarcoma, CT= computed tomography, MRI= magnetic resonance imaging, US = Ultrasound Scan

## Introduction:

Chronic Fibrocalculus pancreatitis with mass lesion, often creates a diagnostic dilemma resulting into therapeutic uncertainty. Although these are commonly chronic inflammatory fibrotic lesions but in 4% cases associated with pancreatic malignancy and up to 18% in endemic zone. Resection is the gold standard. Malignant tumor composed of malignant epithelial and sarcomatous components are labelled as Sarcomatoid carcinoma (SC) and carcinosarcoma (CS). It is a high-grade epithelial malignancy composed predominantly or exclusively of spindle cells demonstrating evidence of epithelial descent. It may occur in many organs, including the breast, lung, uterus, urinary bladder, skin, head and neck, pancreas and prostate. However, SC in pancreas is very rare and not well documented in literature.[1-4] As it is a rare disease, few of the case reports were published with clinical profiles and management in our country.[5-6] The study aims to evaluate the clinical profile of Sarcomatoid carcinoma of pancreas in patients with pancreatic stone disease presenting with mass lesion with outcome after surgery.

## Materials and Methods:

This retrospective multicenter observational study conducted on 12 patients of pancreatic stone disease, operated between June 2000 to January 2017 (17 yrs) in BIRDEM General Hospital and other hospitals of Dhaka performed by teams following the same surgical principle. Patients were included irrespective of their age, sex, mode of presentation and diabetes status. All had pancreatolithiasis, presented with mass lesion. They were thoroughly evaluated and prepared for Surgery. Plain X-ray abdomen (antero-posterior and lateral view), Ultrasound scan, Computed Tomography Scan (CT-scan), Magnetic Resonant Cholangiopancreatogram (MRCP) and tumor markers (Carbohydrate Antigen CA 19-9, CEA) were the modalities of evaluation. Preoperative and intraoperative findings were correlated regarding the stage of disease. They all were operated accordingly and detected anaplastic carcinoma, the sarcomatoid carcinoma on histopathological study of specimen and/or shave or wedge biopsy. All received adjuvant chemotherapy, followed-up for a maximum period of 22 months.

## Results:

**Table 1:** Distribution of Age Group and Sex of patients (n=12)

| A) Age group in years | No. of patients | Percentage |
|---|---|---|
| 30-39 | 2 | 16.6 |
| 40-49 | 5 | 41.6 |
| 50-59 | 3 | 25 |
| 60-69 | 1 | 8.4 |
| 70-79 | 1 | 8.4 |
| **B) Sex** | **No. of patients** | **Percentage** |
| Male | 7 | 58.3 |
| Female | 5 | 41.7 |
| Total | 12 | 100 |

We came across 12 such cases of pancreatolithiasis presented with mass lesion. All of them were detected as Sarcomatoid carcinoma. Five patients (41.6%) were between 40-49 years' group, 07 were male (58.3%) and 05 were female (41.7%) as shown in Table 1A & 1B.

**Table 2:** Clinical profile of the patients (n=12)

| Symptoms | Number of patients | Percentage |
|---|---|---|
| Abdominal pain | 12 | 100 |
| Vomiting | 12 | 100 |
| Steatorrhoea | 10 | 83.33 |
| weight loss | 12 | 100 |
| Jaundice | 8 | 66.6 |
| Backache | 5 | 41.6 |

All 12 patients of chronic fibrocalculus pancreatitis presented with mass lesion and different degree of pancreatic insufficiency. All patients presented with recurrent upper abdominal pain, vomiting, weight loss and 10 (83.3%) patients with steatorrhoea (Table 2). Eight patients (66.6%) presented with clinical features of obstructive jaundice with palpable gall bladder. Besides abdominal pain, 05 patients also had severe backache (41.6%).

**Table 3:** Tumor location in Pancreas (n=12)

| Tumor location in pancreas | No. of patients | Percentage |
|---|---|---|
| Head | 01 | 8.3 |
| Head and body | 05 | 41.6 |
| Body and tail | 4 | 33.3 |
| Whole pancreas | 2 | 16.7 |

All had extensive pancreatic stones in head and body region. They were assessed and evaluated thoroughly, preoperative and intraoperative findings were analyzed and correlated. Five patients (41.6%) presented with mass lesions in head-body region, 04 in body-tail region Five patients (41.6%) presented with mass lesion in head-body region, 04 in bodytail region and in 02 (16.7%) in the whole pancreas. Only 01 patient had a pancreatic head mass, who was in early stage of disease (Table 3).

**Table 4:** Extent of the disease (n=12)

| Stage | No. of patients | Percentage |
|---|---|---|
| Early | 1 | 8.4 |
| Locally advanced | 6 | 50 |
| Advanced ( metastasis) | 5 | 41.6 |
| Total | 12 | 100 |

Out of 12 patients, 06 patients (50%) were locally advanced and 05 (41.6%) were metastatic disease (Table 4).

Plain X-ray abdomen (antero-posterior and lateral view), Ultrasound scan, CT-scan and MRCP were the modalities to evaluate pancreatic stone disease, locate the mass lesion and staging.

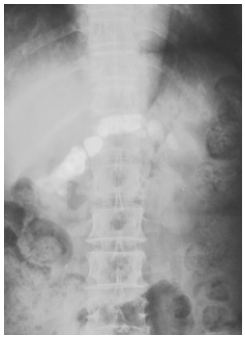
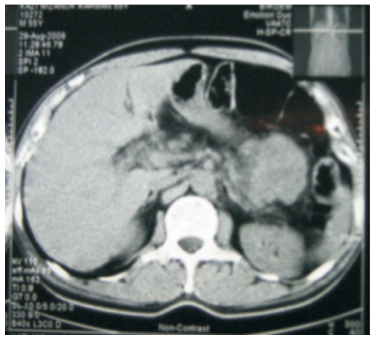


**Fig.** 1A



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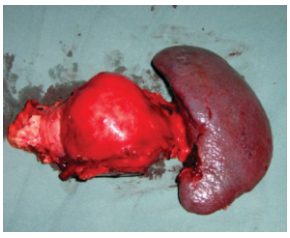

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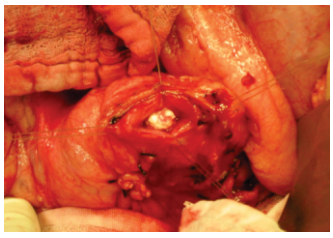

**Fig.** 1D

Figure 1: A) Plain X-ray of abdomen showing Pancreatolithiasis; B) CT scan of abdomen showing distal pancreatic mass; C) Resected en-mass specimen of distal pancreas with spleen; D) Remaining pancreas with a large stone in the pancreatic duct

Observation 1: A 52 years' diabetic gentleman presented with pancreatic calculi and a mass lesion of 6.5x5x5cm in the body-tail region of pancreas CECT-scan. FNAC was positive for malignant cells. He underwent Distal Pancreatectomy en-mass with Spleenectomy along with Pancreatolithotomy and Roux-en-Y Pancreato-jejunostomy along with hepatic metastetectomy in segment (Fig.1)

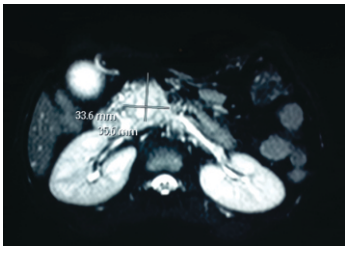

**Fig.** 2A

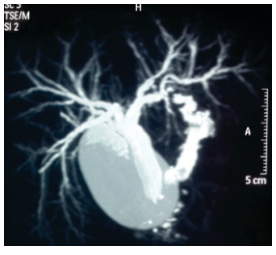

**Fig.** 2B

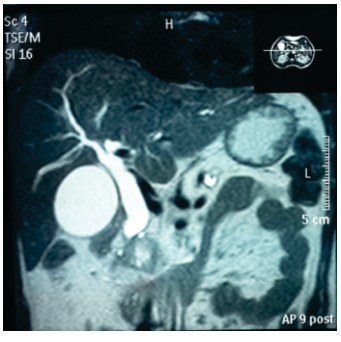

**Fig.** 2C

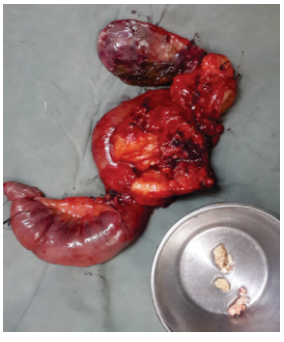

**Fig.** 2D

Figure 2: A) MRI: Horizontal section of tumor B) MRCP: Double duct sign with distended Gall bladder. C) MRI coronal Section: Stone with tumor and dilated biliary tree D) Whipple's partial pancreaticoduodenectomy specimen with opened up tumor and stones

Observation 2: According to operative findings planned lateral pancreaticojejunostomy was converted to Whipple's partial Pancreaticoduodenectomy with mesopancreas. A 30 years' homemaker, nondiabetic lady, detected as Pancreatolithiasis 3 years back, presented with upper abdominal pain and pancreatic insufficiency for three months. MRCP revealed multiple calculi within dilated main pancreatic duct MPD (9mm) and moderately dilated biliary tree and gall bladder. A 4x3 cm mass lesion of was detected in pancreatic head without Lymphadenopathy and liver metastases. Partial pancreatico-duodenectomy done along with mesopancreas, stomach antrum, and around 15 cm of proximal jejunum. Pancreatico-jejunostomy (side to side over a stent), Hepatico-jejunostomy (end to side), Gastro-jejunostomy (end to side), Jejuno-jejunostomy (side to side) were performed accordingly (Fig: 2). She had uneventful postoperative recovery now on adjuvant chemotherapy.

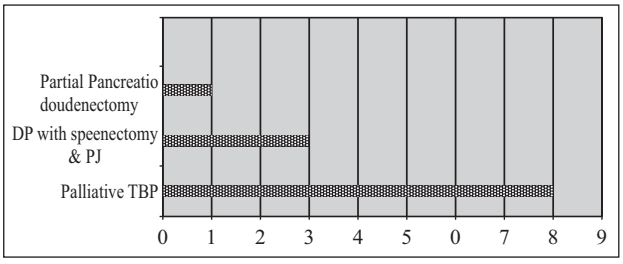


**Fig. 3:** Distribution of operative procedures (n=12)

Among the 12 patients only 04 cases (33.3%) were resectable; only one case (8.33%) was resectable to whom Whipple's Partial pancreatico-duodenectomy was done. In three patients (25%) who had mass lesion in the body and tail region were locally advanced tumors, palliative Distal Pancreatectomy with Spleenectomy was done (Fig: 3). Eight (66.6%) underwent Palliative Triple bypass (Gastrojejunostomy with Roux en Y Hepaticojejunostomy) with Pancreatic biopsy. Pacreaticolithotomy was possible only in 04 patients (Fig 3).
Histopathological specimen of all 12 cases were studied.

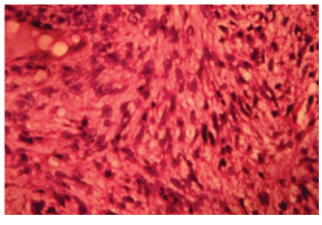

**Fig. 4:** Histopathology of distal pancreatic lesion Sarcamatoid carcinoma

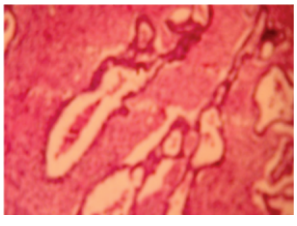

**Fig. 5:** Histopathology of hepatic metastatic adenocarcinoma

Pancreatic shave/ wedge biopsy was obtained in 08 cases of irresectable tumors, 03 patients had distal Pancreatectomy Spleenectomy and only 01 case of partial pancreaticoduodenectomy specimen of resectable cases were analyzed. The cut section of pancreatic in resected specimen's distal pancreatectomy specimen showed tumor mass occupying the body and tail. The spleen was unremarkable on gross examination. Multiple lymph nodes were identified in the splenic hilar tissue. Microscopic examination revealed malignant neoplasm consisted of anaplastic epithelial cells arranged in glands and clusters. A large proportion of tumor cells were spindle shaped and present diffusely forming a Sarcomatoid appearance

(Fig.4). Due to marked heterogeneity on microscopic examination anaplastic carcinoma of pancreas are subdivided into three basic histological subtypes: spindle cell carcinoma, pleomorphic carcinoma and round cell carcinoma. In our case, the majority of cells are spindle shaped forming a Sarcamatoid appearance. The splenic hilar lymph node showed of metastasis in all 03 patients. In 01 patient liver nodule showed a metastatic tumor containing malignant cells arranged diffusely. In case of Whipple's partial pancreaticoduodenectomy, tumor in the pancreatic head region was removed en-mass with attached fibro fatty tissue along with multiple stones. Presence of plenty of spindle cells along with glandular structures & areas of clear-cut glandular differentiation in Sarcomatoid Carcinoma was diagnostic. Resection margins were free of tumor invasion. The Hepatic nodule revealed metastatic adenocarcinoma with hepatic margin free of tumor invasion (Fig.5). In case of Whipple's partial pancreaticoduodenectomy, tumor in the pancreatic head region was removed en-mass with attached fibro fatty tissue along with multiple stones. Presence of plenty of spindle cells along with glandular structures & areas of clear-cut glandular differentiation in Sarcomatoid Carcinoma was diagnostic. Resection margins were free of tumor invasion and 3 out of 7 node showed metastasis.

Perioperative analgesia and good glycemic control was a challenge. However, postoperative epidural analgesia for first 3 to 5 days showed encouraging results.

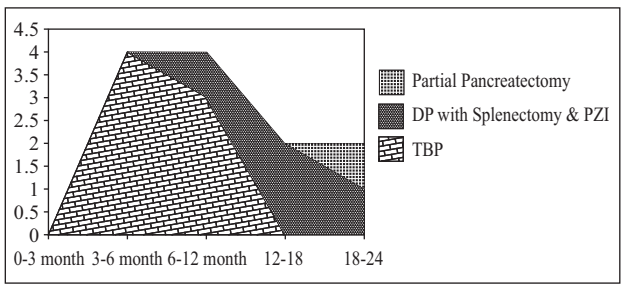


**Fig. 6:** Duration of Survival after surgery

All 12 Patients had uneventful recovery in the immediate postoperative period and without any 30 days' postoperative morbidity or mortality except three who had right sided basal atelectasis and was treated conservatively. All received adjuvant chemotherapy with standard regime including gemcitabine by the oncologist. All the 12 patients were followed up for a maximum period of 22 months. The 08 patients to whom palliative triple bypass were done, only three survived up to one-year rest 05 patients died within six months of surgery (Fig 6). However, the quality of life was improved and was better than before. Surgery also showed improved quality of life with better survival in 03 patients of distal pancreatectomy with Spleenectomy.

**Table 5:** Survival following surgery (n=12)

| Survival ( months) | Number of patients | Percentage |
|---|---|---|
| 5-9 | 6 | 50 |
| 10-14 | 3 | 25 |
| 15-19 | 2 | 16.7 |
| 20-24 | 1 | 8.3 |

Study revealed only 06 (50%) patients survived for only 5 to 9 months, followed by 3 patients (25%) for 10 to 14 months (Table 5).

However, surgery improves the quality of life but with survival benefits. We found Sarcomatoid carcinoma, an aggressive malignancy and advanced disease at the time of presentation. It has a gloomy outcome. However, the above curative resection it showed, improved quality of life and increased survival benefit with the hope of cure.

## Discussion:

Chronic Fibrocalculus pancreatitis is a disease of remission and relapse. When presents with a mass lesion it often causes diagnostic dilemma and therapeutic uncertainty. These are commonly chronic inflammatory fibrotic lesions, but in 4% cases associated with pancreatic malignancy and 18% cases in endemic zone.[7-9] Pancreatic Malignancy is the 10th cause of cancer and fourth common cause of cancer related death in USA.[10,11]

Sarcomatoid carcinoma (SC) and carcinosarcoma (CS), also known as anaplastic carcinomas or undifferentiated carcinomas, giant cell carcinoma, pleomorphic large cell carcinoma, spindle cell carcinoma. The etiology is unknown. During malignant progression, carcinoma cells undergo Epithelial-to-Mesenchymal transition, a vital step in pancreatic ductal adenocarcinoma formation.[11-14] Aggressive clinical course with biphasic epithelial and mesenchymal differentiation is significant. The incidence is only about 2% - 7% of all pancreatic cancers.[12-13] In our previously published series the incidence was 4.7%.[10] Our present series comprises of 12 such cases Sarcomatoid carcinoma, who earlier detected pancreatic stone disease presented with mass lesion(s), between the ages of 30 to 79 yrs. Seven were male (58.3%) and five were female (41.7%). We found 5 patients (41.6%) were between 40 - 49yrs group (Table 1). Recurrent upper abdominal pain, vomiting, steatorrhoea, Loss of appetite, nausea, vomiting, weight loss and diarrhoea are the usual clinical symptoms. Eight patients (66.6%) with features of obstructive jaundice with palpable gall bladder with backache (41.6%) as in Table 2.

Current literature review revealed, there is no specific radiologic diagnostic feature of this entity, but may be considered as differential of a mixed solid-cystic pancreatic mass.[13, 14] Traditionally, the use of preoperative imaging and endoscopic modalities, in combination with

intraoperative findings and pathologic evaluation, has guided the surgeons to perform the correct operative procedure. Tumor markers, CEA and CA 199 have neither the sensitivity nor specificity as broad screening markers. Multi-phase intravenous contrast directed thin slice computed tomography (CT-scan) and magnetic resonance imaging (MRI) allow accurate characterization of the lesions, tumor resectability, relation of tumor to visceral vessels and extra-pancreatic dissemination. Endoscopic ultrasound (EUS) and Endoscopic retrograde cholangio-pancreatography (ERCP) are important for workup.

In our series, Plain X-ray abdomen (antero-posterior and lateral view), Ultrasound scan, CT-scan and MRCP were the modalities to evaluate pancreatic stone disease and mass lesion including staging. They were thoroughly assessed, 05 patients (41.6%) presented with mass lesion in head-body region, 04 in bodytail region and in 02 patients it involved the whole pancreas. Only 01 patient had a pancreatic head mass (Table 3) and in early stage of the disease, 06 (50%) with locally advance and 05 (41.6 %) in advanced disease (Table 4). Anaplastic carcinoma of pancreas is aggressive in nature with rapid direct Iocoregional spread. Literature review revealed tumors of body and tail are more likely to give pulmonary rather than hepatic metastasis. In our series 41.6% patient had hepatic metastasis without any pulmonary metastases. Among the 12 patients, only 04 cases were resectable (33.3%). Three patients had mass lesion in the body and tail region under gone palliative resection in the form of Distal Pancreatectomy with Spleenectomy followed by pacreaticolithotomy and end to side Roux-en-Y Pancreaticojejunostomy (Fig 3). Only one was lucky to have curative resection (8.33%), to whom Whipple's Partial pancreaticoduodenectomy was done. Rest of the 08 patients, Pancreatic biopsy and palliative triple bypass in the form of Gastrojejunostomy, Roux-en-Y Hepaticojejunostomy was done. Pacreaticolithotomy was not possible in those patients (Fig 3). Three patients developed right sided basal atelectasis in the post-operative period and was treated conservatively. However, rest of the patients had uneventful recovery, without any 30 days postoperative morbidity or mortality and all received adjuvant chemotherapy.

Sarcomatoid carcinoma (SC) and carcinosarcoma (CS), is an epithelial malignancy associated with Sarcomatous (spindle cell) component. It has been reported in different organs, very rare in pancreas. These are anaplastic carcinomas or undifferentiated carcinomas, also known as giant cell carcinoma, pleomorphic large cell carcinoma, spindle cell carcinoma. The tumor demonstrated cellular patterns similar to those present in tumors of mesenchymal origin these tumors are large exophytic, heterogeneous, solid with cystic masses with areas of necrosis and hemorrhage on gross pathological examination. They are subdivided into three basic histological subtypes: spindle cell carcinoma, pleomorphic carcinoma and round cell carcinoma. In our case, the majority of cells are spindle shaped forming a Sarcomatoid appearance. We also observed areas of ductal adenocarcinoma in situ, conjunctions between the carcinomatous and sarcomatous areas, and focal desmosomal cell junctions in the sarcomatous areas. The sarcomatous components were hypercellular, and in contrast to the carcinomatous areas. Besides, World Health Organization (WHO) classified pancreatic tumors, defined undifferentiated (anaplastic) carcinoma as a combination of 3 variants of ductal adenocarcinoma, i.e., giant cell carcinoma, pleomorphic large cell carcinoma, and Sarcomatoid Carcinoma.[15,16] We found presences of both carcinomatous and sarcomatous components, support the current concept. Immunohistochemical staining is the key to determining the origin of tumor cells and distinguishing them from metastatic carcinoma, malignant melanoma, rhabdomyosarcoma, choriocarcinoma, Anaplastic large cell lymphoma and epithelloid sarcoma. SC commonly shows pan-cytokeratin expression, but in mucinous neoplasm with coexisting sarcomatous stroma it lacks keratin immunoexpression and show evidence of mesenchymal differentiation.[16]

Sarcomatoid carcinoma of pancreas has poorer survival compared to invasive ductal adenocarcinoma. There is limited data available on treatment options for these tumors. Compared with other pancreatic carcinomas. Malignant giant cell tumors of pancreas appear to have a characteristics of local invasiveness, a reluctance to metastasize, highlighting more favorable prognosis when resected.[13,14,17] Sarcomatoid carcinoma is an aggressive malignancy, at the time of presentation. Literature review suggests, high levels of NSE, TGFβ1, and IL-11 in the serum or plasma may help in early diagnosis. TGFβ1 may play an important role in tumor metastasis.[17] Curative resection is usually not always possible due to aggressive and extensive nature of the disease at presentation with early recurrence.[18]

Among the 08 patients palliative triple bypass only three patients survived up to one year, rest 05 patients died within six months. Among the 03 patients of distal pancreatectomy with Spleenectomy and Pancreaticojejunostomy after Pancreatolithotomy showed improved quality of life and survival. Two of them survived more than a year up to 14 months, one patient died in his 21st month of surgery and another survived up to 11 month of surgery. The lady who under gone partial pancreaticoduodenectomy on her 22nd month of surgery and adjuvant chemotherapy without any recurrence. The study revealed survival benefit with improved quality of life after surgery. This study showed 50% patients survived for only 5 to 9 months (Table 5). We can conclude that, Sarcomatoid carcinoma is a rare disease with aggressive nature and has got gloomy outcome. However, in patients with curative resection it showed, improved quality of life and increased survival benefit.

## Conclusion:

Sarcomatoid carcinoma of pancreas is a rare pancreatic malignancy. High index of suspicion is essential for early diagnosis. It is a highly aggressive malignancy with dismal prognosis. Resection is the gold standard management strategy in early stage and gives hope of cure. Although some have rapid recurrence and an early demise, long-term survival may be possible. Future studies are needed to better define the cohort with potential for long-term survival. So that, aggressive management can be tailored appropriately for this aggressive malignancy.

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# Original Article

# Correlation of Stature with Great Toe Length and Breadth from Footprint of Bangladeshi Male Medical Students

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## Abstract

**Background**: Foot dimension has great use in anatomy, physiology, ergonomics, forensic science, plastic surgery, radiology, podiatry, archaeology, anthropology, nutrition science and diagnostic knowledge between patient and normal population. The data of foot dimensions of Bangladeshi male is essential for the anatomist for normative reference, to the radiologist and podiatrist for diagnosis of diseases in their respective fields. Stature can be correlated from foot dimensions using different foot segments from footprints**.**

**Objective:** This cross sectional study was planned to determine the different dimensions of the footprint of the Bangladeshi males and to find out the correlation of stature with foot dimensions from footprint of Bangladeshi male medical students.

**Methods:** Two hundred (200) male medical college students of 18-25 years of age were selected from different medical colleges of Dhaka city and their age was determined by their national ID cards. Stature was measured using a stadiometer. Both feet of the same individual were painted with ink with the help of the brush. After ensuring that toes and sole were inked properly, footprints were taken at the same time for both feet while the ink was still wet.Length of differenttoes were then measured in centimeter from the footprints using a Vernier digital spreading caliper.For statistical analysis, SPSS version 16 was used.

**Results:** In the present study, significant differences were observed between big toe length and breadth of both feet. Big toe pad length and breadth of right foot was greater than the left foot. There was a strong correlation between the stature and big toe length and breadth among Bangladeshi males ($P<0.001$).

**Conclusion:** Big toe pad length and breadth were significantly higher on the right footprint than the left footprint of Bangladeshi male medical students. Further studies with larger sample size are recommended to get more precise picture in order to produce a more comprehensible data that will help to determine the correlation of stature with dimensions of footprint of Bangladeshi medical students.

**Keywords:** Stature, Big toe length, Big toe breadth, Footprint, Male Medical Students.

## Introduction:

Every part of human body is unique in itself as every part of the body is different in its own way from a similar part in another body. There is also a relationship between each part of the body and the whole body. Footprint is the impression of the sole of the foot on an even flat ground or surface which provides the size dimensions of the plantar surface of the foot actually touching the floor or a hard surface.

Footprints are of immense value in establishing personal identity of the criminals in forensic examinations. The partial or complete footprints can be found on rain covered areas, newly waxed floors, freshly cemented surfaces, moistened surfaces, in dust, mud, sand, oil, paint and can be left in blood at the crime scenes.[1] The foot dimensions derived from footprint can provide definitive information on many physical characteristics of the individual as morphology of human foot shows variations due to the combined effects of heredity, lifestyle and climatic factors.[2]

Assessing the height of an individual from measurements of different dimensions ofthe foot has always been of immense interest to anatomists, anthropologists, podiatrists and industrialists involved in designing foot wears. It has been shown that the reliability of prediction of stature from foot dimensions is as high as that from long bones. Foot or shoe prints, if present at the scene of crime, may provide clue regarding the stature of the person which may help in

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establishing partial identity of the suspect. Moreover, in an aircraft accident it is the feet, which are recovered more intact than other parts of the body, as they are often shoe clad.[3] As ossification of the bones of the foot occurs earlier than the long bones of the lower extremity, therefore even during adolescence, stature can be predicted more accurately from foot measurements than that from the long bones of the lower limb.[4] This would enable forensic scientists to solve crimes in the absence of complete evidenceand the anthropologist and archeologist to analyze events that occurred in remote past.[5] Reliable anthropometric data for a target population are necessary when designing foot wears for that population, otherwise the product may not be suitable for the user.[6]

The stature was estimated from skeleton by anatomical method which was introduced by Dwight in 1894.The vertical height of a person needs an equally firm base to support it, which is provided by feet.[7] This provides information that increase in height is associated with an increase in foot dimensions.Estimation of stature from toe lengths in a footprint are of utmost importance as they are strongly correlated with stature and thus gives a better prediction of stature than correlated with other measurements.[8] The foot has been used to estimate stature in several studies in different tribal groups, where normograms have been derived to reconstruct stature from foot dimensions. These types of studies in different communities become essential, as several factors which include genetic and environmental, are known to affect stature and foot morphology as well as dimensions.[9]

The values of different dimensions of foot of Bangladeshi males may be helpful to the anatomists for a normative reference. For the radiologist and the podiatrists the normative values may be helpful in diagnosis of diseases in their respective fields.[10] This knowledge of different foot dimensions and its correlation with the stature is of extreme importance for the forensic scientists to establish the identity of an individual. For proper designing of a prosthetic foot by the ergonomists and for surgical reconstruction by the plastic surgeons foot dimension data is essential.[11]

The present study includes big toe length and breadth from footprint rather than taking length and breadth of whole foot only as have been done in most of the previous studies. So, the study will be applicable to estimate stature from even partial footprint of an individual. With the above perspective, the present study was carried out to give the overview of foot dimensions of Bangladeshi males and to correlate the foot anthropometric data with stature of the same age group of Bangladeshi males.

## Material and Methods:

This cross sectional study was carried out at Department of Anatomy of Dhaka Medical College, Dhaka from July 2012 to June 2013. The study was performed on 200 male Bangladeshi medical students of age ranging from 18-25 years. individuals with congenital anomaly of feet, any deformity of feet from any disease, endocrine diseases like acromegaly, gigantism, those who have encountered any road traffic accident or burn injury affecting feet and tribal population were excluded from the study.

Stature was measured in centimeter according to standard procedures using a stadiometer. The feet of the individual were then washed with liquid soap before inking. Feet were washed to remove oily or greasy substance and dirt from the foot. The feet were then wiped with a towel. Two legal size white papers were fixed on a clip board with double clips to take print of right and left foot which was placed on an even floor as footprints of both feet were collected at the same time. A small amount of ink was poured into a clean and dry flat box with a wide base. The individual was asked to sit on a chair and rest his legs on a low stool with extended knee so that his feet were placed beyond the stool for proper painting of the soles. A wide paint brush was moved in the ink over flat surface of the wide based box until the ink spread thinly and homogenously in the brush.

The right and left foot were painted with ink with the help of the brush. After ensuring that toes and sole were inked properly, footprints were taken at the same time for both feet while the ink was still wet. The feet were carefully removed from the stool and the soles were placed slowly on the paper from proximal to distal end while the individual still remained seated. The individual was then asked to stand from sitting position with his feet placed on the papers on the clipboard without moving the feet. After ensuring that the feet were placed properly the individual was asked to stand erect withoutany support while putting equal pressure on both foot without moving their position on the papers. The individual was then asked to sit. The feet were then lifted from the paper at the same time so that there was no overlapping of the already imprinted footprint. A sharp 2B lead pencil was used to mark the length and breadth of the bog toeat their maximum distant points.

The big toe pad length was measured from anterior terminal landmark (d1t.fp) of the big toe to the posterior terminal landmark (d1.ps.fp). The big toe pad breadth was measured from d1.pm.fp on medial side to d1.pl.fp on the lateral side of the big toe.The vernier digital spreading caliper was placed horizontally on the landmarks and all the measurements were taken in centimeter (Fig.1).

For statistical analysis, SPSS version 16 was used. The relationship between the big toe length and breadth from right and left footprint measurements were determined by paired t- test . Stature was correlated with the big toe length and breadth by Pearson's correlation coefficient test. The study was approved by Ethical Committee of Dhaka Medical College.

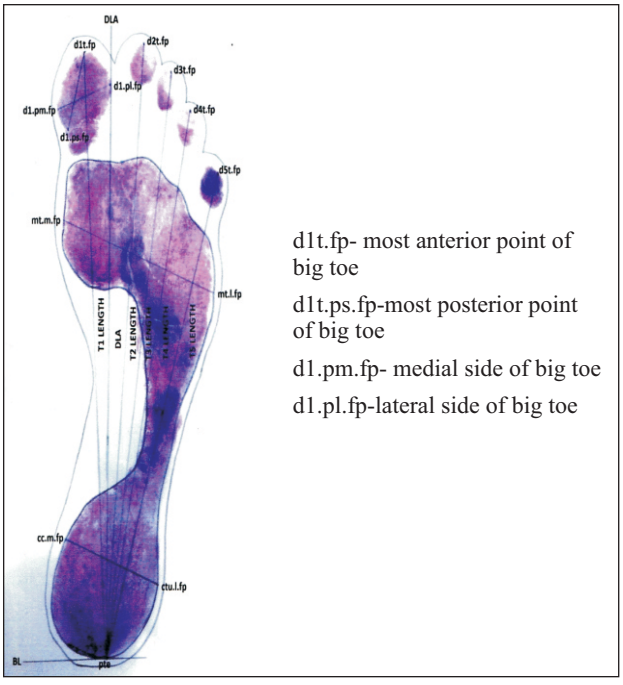


**Fig 1:** Showing footprint landmarks and measurements

## Results:

**Table 1:** Big toe pad length and breadth of right and left footprints of Bangladeshi males

| Foot variables | Length/breadth (cm) | | *p value* |
|---|---|---|---|
| | Right foot (n=200) Mean±SD | Left foot (n=200) Mean±SD | |
| Big toe pad length (d1t.d1ps.fp) | 2.97±0.28 (1.96-3.90) | 2.90±0.26 (2.25-3.68) | 0.0001*** |
| Big toe pad breadth (d1.pm-d1.pl.fp) | 2.59±0.20 (2.05-3.38) | 2.54±0.20 (2.00-3.02) | 0.0001*** |

Figures in parentheses indicate range. Comparison between right and left foot done by paired Student's 't' test, *** = significant at p<0.001

Big toe pad length (d1t.-d1ps.fp) of right and left foot ranged from 1.96-3.90 cm and 2.25-3.68 cm respectively and the mean (±SD) was 2.97±0.28 cm and 2.90±0.26 cm respectively. Difference between big toe pad length of right and left foot were highly significant (P < 0.001)

Big toe pad breadth (d1.pm-d1.pl.fp) of right and left foot ranged from 2.05-3.38 cm and 2.00-3.02 cm respectively and the mean (±SD) was 2.59±0.20 cm and 2.54±0.20 cm respectively. Difference between big toe pad length of right and left foot were highly significant (p< 0.001) as shown in Table 1.

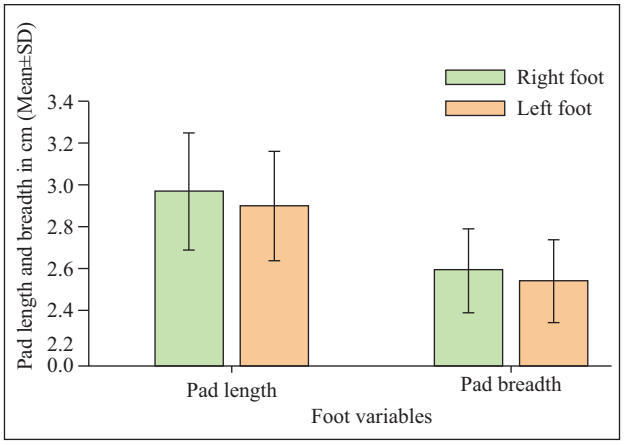


**Fig 2:** Big toe pad length and breadth of right and left footprint of Bangladeshi males

**Table 2:** Relationship between stature and big toe pad length and breadth of right and left footprint of Bangladeshi males

| Foot variables | Right foot (n=200) | | Left foot (n=200) | |
|---|---|---|---|---|
| | r value | p value | r value | p value |
| Big toe pad length (d1t.d1ps.fp) | +0.261 | 0.0001*** | +0.283 | 0.0001*** |
| Big toe pad breadth (d1.pm-d1.pl.fp) | +0.259 | 0.0001*** | +0.255 | 0.0001*** |

Pearson's correlation-coefficient (r) test was performed to compare relationship between parameters, *** = significant at p<0.001

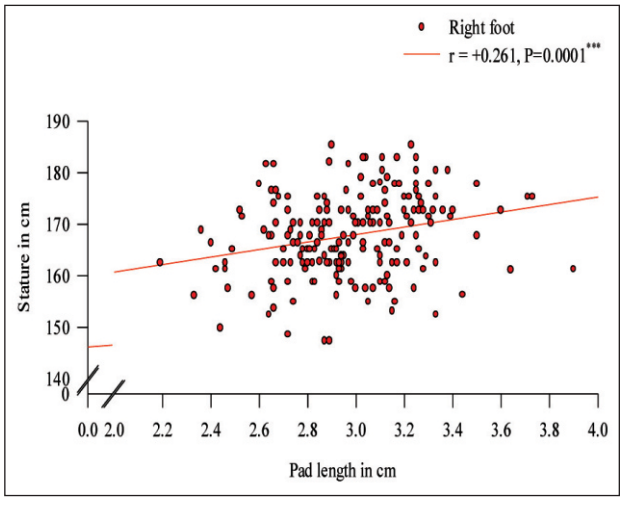


**Fig 3 a:** Relationship between big toe pad length of right and left footprint and stature of Bangladeshi males

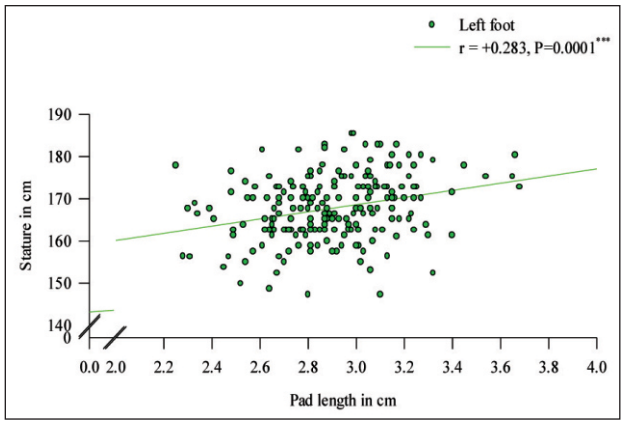


**Fig 3 b:** Relationship between big toe pad length of right and left footprint and stature of Bangladeshi males

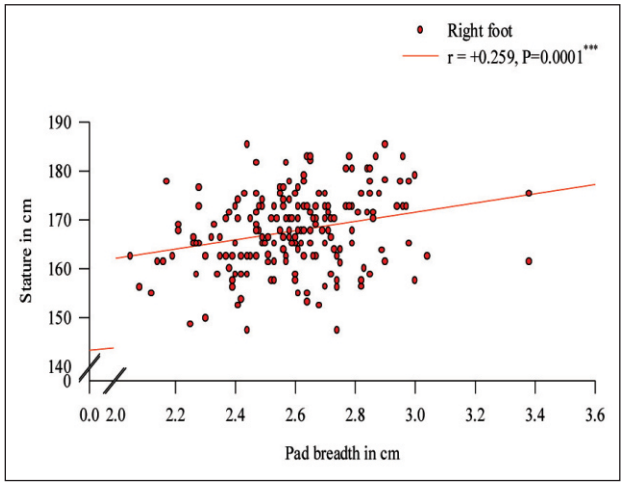


**Fig 4 a:** Relationship between big toe pad breadth of right and left footprint and stature of Bangladeshi males

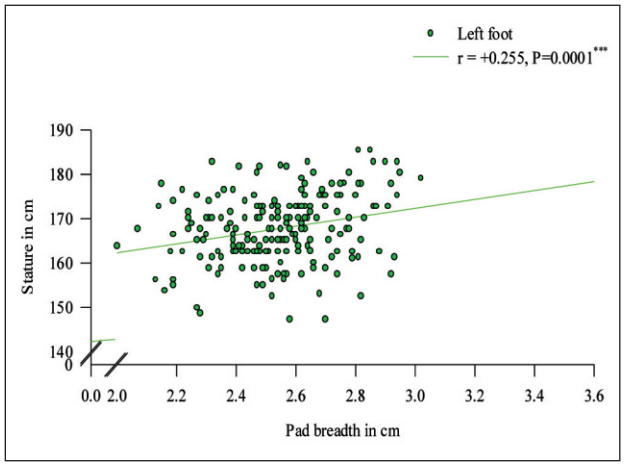


**Fig 4 b:** Relationship between big toe pad breadth of right and left footprint and stature of Bangladeshi males

Relationship between stature and big toe pad length and breadth of right and left footprints of Bangladeshi males:

Correlation of stature with big toe pad length of right and left footprints (Table 2, Fig 3)

Big toe pad length (d1.t-d1ps.fp) of right and left foot were compared with stature and the **r** value was +0.261 and +0.283 respectively. There was a highly significant correlation between the big toe pad length of right and left foot with the stature ($p<0.001$).

Correlation of stature with big toe pad breadth of right and left footprints (Table 2, Fig 4)

Big toe pad breadth (d1.pm-d1pl.fp) of right and left foot were compared with stature and the **r** value was +0.259 and +0.255 respectively. There was a highly significant correlation between the big toe pad breadth of right and left foot with the stature ($p< 0.001$).

## Discussion:

The present work was undertaken to study foot length from footprint of 200(two hundred) medical college students of Dhaka city and describes a statistically based analysis that illustrates the usefulness of the footprint as an indicator of correlation of stature of an individual. The footprints of the present study were collected from the Department of Anatomy of Dhaka Medical College, Dhaka and other non-government medical colleges in Dhaka city. The main aim of the study was to find out the correlation of stature with great toe length and breadth from footprint of Bangladeshi males. The findings of this study were statistically analyzed and revealed important information about variations in foot dimensions of Bangladeshi males.

Dissimilarities might be due to the use of an age group with a wide range of population which included children, adolescents, adults and elderly and admixture of different races.

The reason of dissimilarities with those of Kewal Krishan[2] might be due to racial variation as he used sample from tribal population who are mostly engaged in the agricultural work all the time, putting more strain on their feet while working in the fields and therefore it is most natural that the foot is more used for walking or weight bearing becomes physically better developed. Another reason of dissimilarity is also supported by Rao and Kotian, cited by Kewal Krishan[2] as they suggested that the difference between left and right footprints in the same individual is not a coincidence but may be explained on the basis of the "dominant foot". Most of the individuals have dominant foot, usually the left one, which always support the body to a greater extent while in standing or in walking. The shoe of this foot wears off at a faster rate than the shoe on the other foot. The bones in the dominant foot are regularly subjected to stronger stress forces like weight bearing pressures, than the bones of the other foot. This in

turn enlarges the bones of the dominant foot and therefore produces a footprint of larger dimension.

In the present study, significant differences were observed between big toe pad length and breadth of right and left foot ($p<0.001$). Big toe pad length and breadth of right foot was greater than the left foot. According to Kewal Krishan[2](2008) big toe pad length and breadth was greater on the right foot than the left foot. Big toe pad length and breadth of his study were significantly higher than the findings of the present study for both feet ($p< 0.001$).

In 1986 Robbins LM[1] reported greater big toe pad length and breadth on the right foot than the left foot. Big toe pad length of both feet and big toe pad breadth of left foot of her study were significantly lower than the findings of the present study ($p< 0.001$) but big toe pad breadth of the right foot was not significant with the findings of the present study ($p>0.005$).

In the present study, correlation of stature with big toe length and breadth from footprint were highly significant ($p<0.001$).

## Conclusion:

In the present study, the big toe pad length and breadth which were significantly higher on the right footprint than the left footprint among Bangladeshi male medical students. There was a strong correlation between the stature and big toe length and breadth from footprint among Bangladeshi male medical students.

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# Original Article

# Helicobacter Pylori Infection Status among Dyspeptic Patients Using Stool Antigen Test

Rana MA[a], Saha M[b], Chowdhury MKS[c], Ara N[d]

## Abstract

**Background:** Detection of Helicobacter pylori (H. pylori) has an important role in the approach to the management of dyspepsia. In Bangladesh, H. pylori detection is mainly done by rapid urease test which is an invasive test needing endoscopy of upper GIT. Stool antigen test (SAT) being a non-invasive and not expensive test, may be an attractive alternative for H. pylori detection.

**Objective:** To assess the burden of H. pylori infection in patients presenting with dyspepsia using Stool Antigen Test. (SAT)

**Methods:** This cross sectional, descriptive type of study was carried out among the patients presenting with dyspepsia in the outpatient department of North East Medical College Hospital, a tertiary care hospital in Sylhet, Bangladesh from January 2016 to July 2016. Total 260 patients were selected by purposive type of sampling. Stool antigen test were carried out by immune chromatography assay (ICA) using standard protocol. Among the study population upper GI endoscopy was carried out among those who gave consent for the same. Statistical analyses were performed using SPSS version 13.0.

**Results:** Among 260 study population, 199(76.5%) were male and 61(%) were female. Mean age was 40.6 ±1.31 years. Epigastric pain was the most common symptom (55.7%), followed by post prandial abdominal fullness (31.9%). Stool antigen test was positive in 96 (37%) and negative in 164 (63%) patients. H pylori was detected in 39% of the male population whereas 29% female tested positive for H pylori by SAT. H. pylori was more common in those with no academic qualification (illiterate) than those having academic qualification (42% vs. 37%). Among 116 patients who underwent endoscopy 95 (82%) had abnormal finding and H. pylori was positive in 39 (33%) patients.

**Conclusion:** This study showed a higher active H. pylori infection in the study population. SATs being cheap and easily done, may be an option to consider in resource poor setting like our country.

**Keywords:** Dyspepsia, Helicobacter pylori, Stool antigen test (SAT)

## Introduction:

Dyspepsia is a common gastroenterological problem with a prevalence of 8 % to 41% in general population of Bangladesh.[1,2] Helicobacter pylori detection has an important role in the approach of management of dyspepsia as it is a common curable cause of peptic ulcer and gastric cancer and is also responsible for 5% cases of functional dyspepsia.[3] The prevalence of helicobacter pylori infection is high in Bangladesh. More than 90% apparently healthy adults have been found to have antibody to Helicobacter pylori in the blood. [4,5]

An important tool for management of dyspepsia is 'Test-and-treat strategy'. This strategy implies that presence of Helicobacter pylori infection should be tested non-invasively and if found positive, should be treated by eradication therapy. It results in cure of H. pylori infection as well as cure of peptic ulcer disease if present. In a number of functional dyspepsia patients, Helicobacter pylori eradication is followed by symptomatic improvement.[5] Endoscopy is thus avoided in a good proportion of patients. Many Western guidelines have recommended that if prevalence of H. pylori infection is high (>10%-30%), patients should undergo test-and-treat strategy. [6-10]

'Test and treat' approach is useful in areas where Helicobacter pylori infection can be diagnosed by non-invasive tests such as urea breath test (UBT), stool antigen test (SAT) and serological test.[5] Serological test doesn't necessarily indicate active infection and is not useful as a test of eradication. Urea breath test and Stool antigen test are preferred non-invasive methods of diagnosing Helicobacter pylori. Urea breath test is costly and commercially available in very limited centers, whereas stool antigen tests do not require expensive chemical agents or specified equipment and so they are less expensive. SATs are useful for primary diagnosis and also for the assessment of eradication therapy.

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In the above background, this study was carried out to find out the burden of H. pylori infection among patients presenting with dyspepsia using stool antigen test for detection of H pylori.

## Materials and Methods:

It was a cross sectional type of descriptive study, carried out among the patients visiting the outpatient department of North East Medical College, a tertiary care hospital in Sylhet, Bangladesh from January 2016 to July 2016. Institutional ethical clearance was obtained for this study. Total 260 patients presenting with dyspepsia were selected by purposive sampling. Adults aged 18 years and above who consented to participate were included in the study. Patient with known hepatobiliary and pancreatic disease, malignancy and on medication likely to cause dyspepsia, or those who received antibiotics, PPI in the previous 4 weeks were excluded from the study. Patient with predominant heartburn as a symptom and alarm features-unintended weight loss, progressive dysphagia, recurrent or persistent vomiting, evidence of GI bleeding, fever, family history of gastric cancer, new onset dyspepsia in a patient over 50 years of age, odynophagia, unexplained iron deficiency anemia, palpable mass or lymphadenopathy were also excluded. Dyspepsia was defined as per Rome III diagnostic criteria as the presence of one or more dyspepsia symptoms (postprandial fullness, early satiation, epigastric pain, and epigastric burning) that are considered to originate from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms.[11] Complete history, physical examination was done in every patient at the entry of the study. Stool antigen test were carried out by immune chromatography assay (CerTest H. pylori one step card test) using standard protocol as per manufacturers instruction. Among the study population upper GI endoscopy was carried out among those who gave consent for the same. Statistical analysis was performed using SPSS version 16.0.

## Results:

**Table 1:** Age and sex distribution of the dyspetpic patients.

| Age in years | Male No. | Female No. | Total No. (%) |
|---|---|---|---|
| 11-20 | 5 | 2 | 7(2.7) |
| 21-30 | 51 | 9 | 60(23.1) |
| 31-40 | 59 | 12 | 71(27.3) |
| 41-50 | 50 | 18 | 68(26.2) |
| 51-60 | 23 | 13 | 36(13.8) |
| 61-70 | 6 | 6 | 12(4.6) |
| 71-80 | 5 | 1 | 6(2.3) |
| Total | 199(76.5%) | 61(23.5%) | 260(100%) |

Among 260 patients with dyspepsia, 199 (76.5%) were male and 61(23.5%) were female. Most of the dyspeptic patients (27.3%) were from 31-40 years' age group (Table 1). Mean age was 40.6 ±1.31 years.

**Table 2:** Pattern symptoms of dyspepsia in the Study population

| Predominant symptom | Frequency (No.) | Percentage (%) |
|---|---|---|
| Epigastric pain | 145 | 55.7 |
| Post prandial fullness | 83 | 31.9 |
| Epigastric burning | 18 | 7.0 |
| Early satiety | 9 | 3.4 |
| Others | 5 | 2.0 |
| Total | 260 | 100 |

Epigastric pain was the most common symptom 55.7%, followed by post prandial abdominal fullness 31.9% (Table 2).

**Table 3:** Sex wise distribution of H. pylori infection (n =260)

| Sex | Total stool samples (n) | H. pylori positive (%) | H. pylori negative (%) |
|---|---|---|---|
| Male | 199 | 78 (39) | 121(61) |
| Female | 61 | 18 (29.5) | 43(70.5) |
| Total | 260 | 96 (37) | 164 (63) |

Stool antigen was positive in 96 (37%) and negative in 164 (63%) of the dyspeptic patients. H. pylori was detected in 39% of the male patients whereas 29.5% female tested positive for H. pylori by SAT (Table 3).

**Table 4:** H pylori infection in different literacy groups (n =260)

| Level of education | Total stool samples (n) | H. pylori positive (%) | H. pylori negative (%) |
|---|---|---|---|
| Illiterate | 45 | 19 (42) | 26 (58) |
| Literate | 201 | 75 (37) | 138 (63) |
| Total | 260 | 96 (37) | 164 (63) |

H. pylori was more common in those with no academic qualification (illiterate) than those having academic qualification (42% vs. 37% as shown in Table 4.

**Table 5:** Status of patients undergoing Endoscopy (n=116)

| A) Endoscopic Findings | No. of patients | Percentage |
|---|---|---|
| Normal | 21 | 18 |
| Abnormal | 95 | 82 |
| Total | 116 | 100 |
| B) H.pylori infection | No. of patients | Percentage |
| H. pylori positive | 39 | 33 |
| H. pylori negative | 77 | 67 |
| Total | 116 | 100 |

Endoscopy of upper GIT was done in 116 patients (44%) out of 260 patients. Among those in 21 (18%) patients no abnormality was found in endoscopy and in 95 patients (82%) gastritis, ulcers and other findings were found (Table 5.A). In those undergoing endoscopy 39 (33%) were H. pylori positive and 77 (67%) were negative.

## Discussion:

In this study most of the patients with dyspepsia, 199 (76.5%) were male and 61(23.5%) were female. Most of the dyspeptic patients (27.3%) were from 31-40 years' age group (Table 1). Average age was 40.6 years. Male female ratio was 3.3:1. In another study 49 (39.2%) were males while 76(60.8%) were females, giving a male to female ratio of 1:1.6. Their ages ranged between 18 and 84 years with a mean age of 35.3± 12.7 years. Majority of the patients with dyspepsia were between the third and fourth decades of life.[12] Study conducted in Ghana showed that the sample population of dyspeptic patients attending the Endoscopy Unit for upper GI endoscopy yielded 242 patients of which 47.5% were females, 52.5 % males.[13]

Epigastric pain was the most common symptom 55.7%, followed by post prandial abdominal fullness 31.9% (Table 2). In a study upon individual symptom evaluation, no difference was found between the groups in regard to the prevalence of epigastric pain, epigastric burning sensation, burping, or bloating, even though the patients with H. pylori presented less frequently with fullness, early satiety, and nausea compared with the non-H. pylori patients. In the analysis of the predominant symptoms together, there was a greater frequency of *e*pigastric pain syndrome between the patients infected with the bacterium compared with those not infected (64.6 vs 54.4%, respectively, p = 0.01, RR 1.51, 95% CI 1.08-2.13), the prevalence of postprandial distress syndrome was similar in the two groups (16.1% cases vs 14.9% controls, p = NS), and there was a greater number of subjects in the non-H. pylori group that presented with overlap of both syndromes (19.3% of the cases vs 30.6% of the controls, p = 0.002).[14]

By SAT, 37% of the study population was positive for H. Pylori (Table 3). This is higher than the cut off recommended for test-and-treat strategy (>10%-30%). Saha et al, showed H pylori infection in 60% of the study population in India by SAT which is much higher than our detection rate.[15] They used EIA (Quantitative Enzyme Immunoassay) for SAT whereas our method was ICA based assay which might be the reason for lower detection rate in our study.

H. pylori was positive in 39% of male and 29.5% of female. An excess of H. pylori prevalence in males has been reported in other studies as well; for instance, Saha et al, Woodward et al. and Gowda et al. observed similar results.[15-17] Another comprehensive meta-analysis of large, population base studies also showed male predominance of H pylori disease.[18]

Low socioeconomic status, overcrowding and unhygienic conditions contribute to the high prevalence of H. pylori infection in developing countries.[19] This study further supports the findings. In this study H. pylori was found more in the illiterate group than those having education (42% vs. 35%) as shown in Table 4, and in those from poor and lower socioeconomic group than those in higher socioeconomic group (38% vs. 34%) which is not shown in results.

Among the H. pylori positive patients who underwent upper GI endoscopy (39 patients), 7 showed no abnormality on endoscopy and 32 showed some abnormality (Table 5). Those with normal findings might represent early stage of H. pylori infection. In H. pylori negative group 80% showed some abnormality of acid peptic disorder in endoscopic examination. So in this study SATs could not predict the likely outcome of endoscopic findings. The endoscopic abnormality in large percentage of H. pylori negative group might be due to decrease sensitivity of ICA assay. EIA might detect more H. pylori positive cases.

## Conclusion:

According to this study stool antigen test showed high prevalence of H. pylori infection in the study population. As H. pylori positivity denotes active infection, these patients are at risk of H. pylori related disease like peptic ulcer disease, gastric carcinoma and MALT associated lymphoma. To detect these patients at risk, SATs being cheap and easily done, may be an option to consider in resource poor setting like our country.

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# Original Article

# Evaluation of Histological Pattern of Lupus Nephritis with Clinical Features in a Selected Tertiary Care Hospital: An Experience of 50 Cases

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## Abstract

**Background**: Lupus Nephritis (LN) is histopathologically evident in most patients with Systemic Lupus Erythematosus (SLE) even those without clinical manifestations of renal disease. The presentation of renal disease in SLE is variable, ranging from clinically silent nephritis to rapidly progressive crescentic glomerulonephritis with acute renal failure. Assessment and management of patients with suspected Lupus Nephritis is greatly facilitated through information obtained by renal biopsy.

**Objectives:** To evaluate co-relation between the histological findings of renal biopsy with clinical findings among patients with lupus nephritis.

**Methods:** This cross-sectional study was carried out at department of Medicine and Nephrology of Bangladesh Medical College Hospital during the period of 2011 to 2015. Total 50 cases were selected by purposive sampling for this study who were both old and new diagnosed cases of SLE. Informed consent was taken from the patients. All demographic, clinical, and histopathological findings of renal biopsy were documented in a preformed structured questionnaire. Data were analyzed by SPSS version 16.0. For relationship among the variables $p<0.05$ was considered as statistically significant.

**Results:** Majority of patients (58.0%) were in 21-30 years age group and were female (90%). The most common clinical presentations of the patients with LN at the time of renal biopsy were edema (86%), arthralgia (72%), hypertension (58%) etc. Most common histopathological class of LN was Class-IV (58%), followed by Class-V (20%) and class III (16%). LN patients presented with edema, hypertension, arthralgia, malar rash had predominant histopathological class IV. Hypertension, hematuria, nephritic-range proteinuria, renal impairment were predominant features of Class IV. The association between proliferative LN (Class III, IV) with hypertension was significant. Edema, oral ulceration, malar rash, arthralgia had no association with proliferative class group.

**Conclusion:** Early diagnosis and prompt institutional care and guideline of appropriate supportive therapy can make a favorable outcome in SLE patient. The emphasis in SLE related glomerular disease prevention programs must be on early identification of patients at risk and appropriate treatment by means of clinical, pathological and renal biopsy clarification as well.

**Keywords:** Systemic Lupus Erythematosus, Lupus Nephritis, Glomerulonephritis, Renal Biopsy.

## Introduction:

Systemic Lupus Erythematosus (SLE) is a chronic, usually lifelong potentially fatal autoimmune disease characterized by unpredictable exacerbation and remission with variable clinical manifestations. Patients with SLE have a spectrum of glomerular disease, different glomerular injury identified within the general category. Severe Lupus Glomerulonephritis is responsible for much of the morbidity and mortality in this disease. The importance of lupus nephritis to practicing nephrologists is that, although rare, a serious disease whose prognosis can usually be improved dramatically by treatment, but for which the treatment is potentially toxic, prolonged, complex, and difficult to plan and carry out. Lupus is defined by its clinical picture, together with antibodies directed against one or more nuclear components, particularly anti-double stranded DNA (dsDNA). It is best regarded as a syndrome, in which a variety of immunologic events may lead to a similar final common pathway, and thus present a similar clinical picture.

William Osler was the first one who described nephritis as a component of systemic lupus erythematosus (SLE). Despite great improvements in the diagnosis and treatment

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of SLE in the past 50 years, nephritis remained the leading cause of death among patients with SLE. Today, lupus nephritis is responsible for growing percentages of cases with end-stage renal failure that need dialysis or renal transplantation.[1] The classification of lupus nephritis has evolved over past 40 years as more lesions were identified and defined. New revers classification preserves the simplicity of the original WHO classification.[2]

The clinical diagnosis of SLE depends on careful and very thorough history of patients, assessment of the presenting clinical features, examination of all the organ systems and selected investigations. Lupus nephritis can mimic almost any morphologic pattern of glomerulonephritis and it is emphasized that the diagnosis of SLE is not based on morphologic features. SLE is usually diagnosed according to the widely accepted criteria of the American College of Rheumatology.[3]

Lupus nephritis, one of the most serious SLE, usually arises within 5 years of diagnosis. Lupus nephritis is histopathologically evident in most patients with SLE, even those without clinical manifestations of renal disease. The symptoms of lupus nephritis are generally related to hypertension, proteinuria and renal failure.[4]

Assessment and management of patients with suspected lupus nephritis is greatly facilitated through information obtained by renal biopsy. A number of changes occur in kidney in the patients with lupus nephritis. The pathologic findings of lupus nephritis are extremely diverse and may occur in all four renal compartments: glomeruli, tubules, interstitium, and blood vessels. On renal biopsy, most frequent finding is class IV lupus nephritis, followed by class V, class III and class II respectively.[5] Prevalence of male lupus is more common in class IV and V than in other classes. Lupus nephritis class I and II may occur in the absence of clinical abnormality. Class V is characterized by nephrotic syndrome which often is persistent, but renal function impairment develops slowly and is rarely severe.[6] Haematuria, massive proteinuria, low albumin, low complement and renal insufficiency are more marked in proliferative lupus nephritis than other histopathological classes.[7]

Considering the above-mentioned facts and unavailability of data about this disorder and its subtypes in our geographical region, we decided to evaluate the clinical and histopathological findings among patients with lupus nephritis.

## Materials & Methods:

This cross-sectional observational study was carried out at the department of Medicine and Nephrology of Bangladesh Medical College Hospital, Dhaka during the period of January 2011 to December 2015. Fifty diagnosed cases (old and new) of SLE with > 4 ARA (American Rheumatism Association) criteria were selected purposively. Inclusion criteria of patients of SLE (with one or more criteria) were: Urinary Total Protein UTP > 0.5 gm/24 hour/1.73m$^2$ body surface area; urinary active sediment - R.B.C and R.B.C cast; renal insufficiency evidenced by serum creatinine =1.5 mg/dl; clinically suspected RPGN or Rapidly Progressive Glomerulo-nephritis). However, clinically SLE not having renal biopsy; patients having bleeding disorders (according to BT, CT report); bilateral small kidneys or single kidney; previously diagnosed patients of SLE having treatment with MMF (Mycophenolate Mofetil) or pulse cyclophosphamide were excluded from study. Informed consent was taken from the patients.

A pre-structured questionnaire was filled up by the physicians. Patients' data such as age, sex, clinical presentation and histopathological result of kidney etc. were documented in the questionnaire. Patients were monitored after hospital admission, during hospital stay and outcome was assessed time to time. Data were presented by tables and diagrams with descriptive frequency. Data analysis was done by using SPSS version 16.0. "p" value <0.05 considered as statistically significant.

## Results:

**Table 1:** Socio-demographic characteristics of the patients (n=50)

| **1. Age Group** | **Frequency** | **Percentage** |
|---|---|---|
| <20 | **7** | **14** |
| 21-30 | **29** | **58** |
| 31-40 | **10** | **20** |
| 41-50 | **03** | **06** |
| >50 | **01** | **02** |
| **Mean ± SD:** 26.7±11.6 Years | | |
| **2. Sex** | | |
| Male | **05** | **10** |
| Female | **45** | **90** |

Table 1 shows that the age range of the study population was 18-52 years. Majority of patients (58%) belonged to age 21-30 years. Out of 50 cases 45 (90%) were female and 5 (10%) were male. Male female ratio was M: F = 1:9. In case of female peak age was =30 years and in male 31-40 years was found as peak age for lupus nephritis.

**Table 2:** Clinical manifestation of disease among LN cases (N=50)

| Clinical manifestation | Number of cases | Percentage |
|---|---|---|
| Edema | 43 | 86 |
| Arthralgia | 36 | 72 |
| Hypertension | 29 | 58 |
| Malar Rash | 28 | 56 |
| Anaemia | 23 | 46 |
| Fever | 23 | 46 |
| Oral Ulcer | 16 | 32 |
| Photosensitivity | 13 | 26 |
| Alopecia | 8 | 16 |
| Discoid rash | 5 | 10 |
| Pericarditis/Pleuritis/effusion | 4 | 08 |

Table 2 shows that most common clinical presentations of the patients with Lupus Nephritis at the time of renal biopsy was edema (86%), followed by arthralgia (72%), hypertension (58%), malar rash (56%), anaemia (46%), fever (46%), oral ulcer (32%), photosensitivity (26%), alopecia (16%), discoid rash (10%) and pericarditis/ Pleuritis/effusion (8%).

**Table 3:** Histopathological classes of LN (according to WHO histopathological classification system)

| Histopathological classes | Number of patients | Percentage (%) |
|---|---|---|
| Class I | 0 | 0 |
| Class II | 3 | 6 |
| Class III | 8 | 16 |
| Class IV | 29 | 58 |
| Class V | 10 | 20 |
| Class VI | 0 | 0 |

Over half of the lupus nephritis (58%) cases were histopathologically classified as class-IV, followed by class V (20%) and class III (16%) were found as frequent category. No class I and classVI patients were found as shown in Table 3.

**Table 4:** Correlation of clinical manifestations and WHO classes (I-VI) of LN

| Clinical manifestations | Histopathological classes | | | | Total (%) N=50 |
|---|---|---|---|---|---|
| | II (n=3) | III (n=8) | IV (n=29) | V (n=10) | |
| Edema | 2 (66.6) | 4 (50) | 29 (100) | 8 (80) | 43 (86) |
| Arthralgia | 3 (100) | 4 (50) | 19 (65.5) | 10 (100) | 36 (72) |
| Hypertension | 0 | 1 (12.5) | 22 (75.8) | 6 (60) | 29 (58) |
| Malar Rash | 2 (66.6) | 0 | 18 (62) | 8 (80) | 28 (56) |
| Anaemia | 0 | 0 | 13 (44.8) | 10 (100) | 23 (46) |
| Fever | 3 (100) | 4 (50) | 15 (51.7) | 1 (10) | 23 (46) |
| Oral Ulcer | 0 | 4 (50) | 7 (24) | 5 (50) | 16 (32) |
| Photosensitivity | 0 | 0 | 4 (15.8) | 9 (90) | 13 (26) |
| Alopecia | 0 | 0 | 4 (13.8) | 4 (40) | 8 (16) |
| Pericarditis | 0 | 0 | 3 (10.3) | 1 (10) | 4 (8) |
| Discoid rash | 0 | 2 (25) | 3 (10.3) | 0 | 5 (10) |

Edema, arthralgia, hypertension, malar rash and fever were found in almost all classes. About 66.6% patients of class II, 50% patients of class III, 100% patients of class IV, and 80% patients of class V had edema. 100% patients of class II, 50% patients of class III, 65% patients of class IV, and 100% patients of class V had arthralgia. No hypertensive patient was found in class II and 12.5% patients of class III, 75.8% patients of class IV, and 60% patients of class V were hypertensive. About 66.6% patients of class II, 62% patients of class IV, and 80% patients of class V had malar rash. Anaemia and photosensitivity was present in majority cases of class V as 100% and 90% respectively; oral ulcer was present mainly in classIII and V patients; photosensitivity, alopecia and pericarditis were absent in class II and Class III patients. Discoid rash was found 25% class III, and 10.3% class IV patients. Present finding on hypertension shows that the in one way ANOVA test the study finding shows that, the *f*-ratio value is 41.12977. "p" value is 0.00001($p<0.001$). So association between hypertension and LN (class IV &V) is statistically significant.

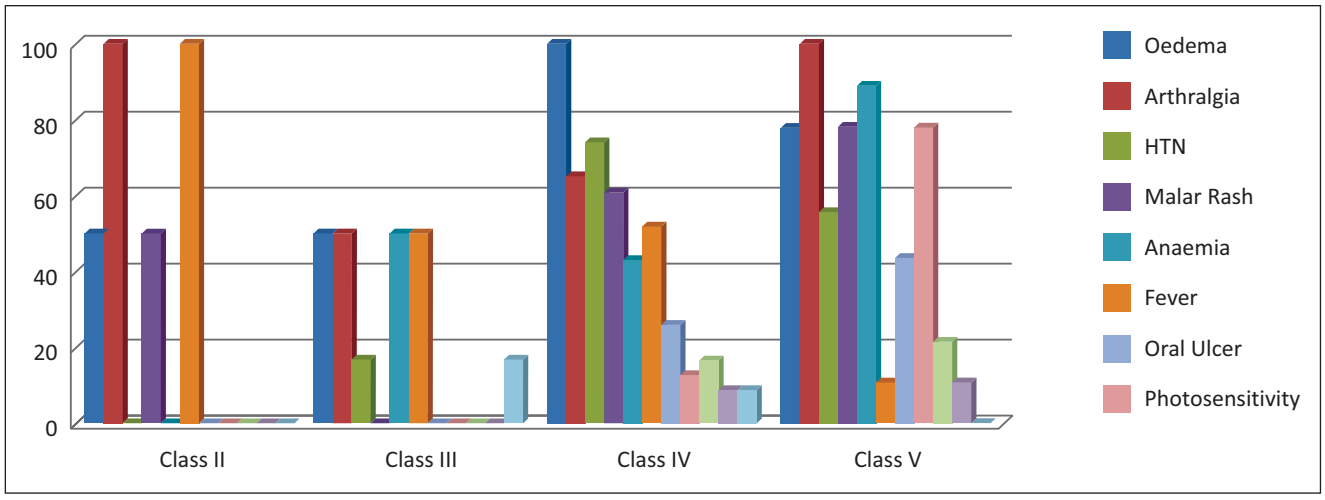


**Fig. 1:** Spectrum of clinical sign symptoms in different classes of LN

In this study, from observation of clinical findings of different histopathological classes of lupus nephritis it was evident that class I and II patients had minimal clinical and renal findings. Edema, hypertension found predominantly in class IV and arthralgia in class II, III and V patients; malar rash mainly observed in class V patients.

## Discussion:

The objective of this study was to find out the correlation of the histopathological finding of renal biopsy to clinical findings of lupus nephritis patients. These issues may be particularly relevant for observational studies that use particular clinical manifestation, histopathological findings.

In this study majority of LN cases were in young age group 21-30 years (58%), next group of patients (20%) observed in 31-40 years of age group and mean age was 26.7 ± 11.6 years (Table 1). Findings are consistent with other studies at home and abroad. Study in a tertiary center of Bangladesh, by Huq MZ[8] reported that mean age was 28.2 ± 7.2 years. Majority of the patients were in 3rd decade (51.6%). Another study at BSMMU in 2006 showed mean age of the Lupus Nephritis patients was 25.5±8.8 years[9]. Similar studies were carried out in Singapore[10] and China[11] showing the mean age of the patient 35.4±8.2 years and 33±14 years respectively. This supports the fact that our patients with Lupus Nephritis were a decade younger than their Chinese counterparts indicating an earlier age of disease onset, more severe form of disease, or earlier mortality in our country.

In this study, out of 50 cases 45 (90%) were female and 5 (10%) were male (Table 1). Male female ratio was 1:9. Huq MZ[8] reported male: female ratio of 1:7.5. Okpechi IG et al in their study in South Africa showed male: female as 1:5.3[12], You SJ et al in a study in Korea showed M: F as 1:12[13]. Current study corroborates with the previous study of Korea but differs with the study carried out in Singapore showing a male: female ratio of 1:4 and another study by Parichatikanond P et al in 1986 where male female ratio was 1:19[14]. This difference could be due to racial and geographical variation of Lupus Nephritis.

Present study shows (Table 2) that most common clinical presentations of the patients with Lupus Nephritis at the time of renal biopsy were edema (86%), followed by arthralgia (72%), hypertension (58%), and malar rash (56%). Among histopathological classes most common (58%) class was IV (n=29), followed by class V 20% (n=10) and class III 16% (n=8) as shown in Table 3.

Huq MZ[8] also demonstrated in his study that most common histopathological class was class IV. The next common classes were class III (20.0%) and class V (18.3%) respectively. In 1991 Halland A M. et al[15] in their study found class IV: 62.7%, class III: 25.4%, class II: 11.7% and class V: 7.8%. Parichatikanond P et al[14] in their study found class IV: 58.6%, class II: 17.9%, class V: 12.9%, class III: 9.9%. You SJ, et al[13] found class IV: 44.8%, class III and V: 22.4% both, class II: 10.4%. Similar frequencies of WHO classification were found by Khoo JJ et al[16] showing 65.7% of their cases belonged to WHO class IV. Another study Gupta RK[17] showed 16.3% belonged to class II, 13.9% belonged to class III and 67.4% to class IV. Hiramatsu et al found the relative frequency of each class were: Class IV: 60%, Class III: 17%, Class II: 13%, Class V: 10%.[18]

Current study shows that edema present in 100% cases of class IV, 80% in class V, 50% in class III and 66.6% in class II. Arthralgia present in 100% of class V and II, 65.5% of cases of classIV. More than 75% of class IV had Hypertension, 50% class V had HTN. Malar rash was in 80% of class V and 62% cases of class IV and not found in class III. Anaemia and photosensitivity were present in majority cases of class V and that is 90% and 80% respectively; oral ulcer was mainly present in class III (50%) and class V (50%) patients. Alopecia, photosensitivity and pericarditis were absent in class II and

Class III patients (Table 4). In a clinic-pathological study on Lupus Nephritis by Huq MZ[8] demonstrated that common clinical presentations were edema and malar rash (73.3% and 70.0% respectively). Kosaraju K et al in 2010 found that 64.58% presented with arthritis as the most common clinical feature[19]. Nezhad ST in 2008 showed common clinical feature are arthralgia (61.8%) and edema (61.1%)[20]. This establishes the fact that clinical manifestations vary according to geographic location of the patients with Lupus Nephritis.

Patient with class IV, V lupus nephritis typically presented with most severe clinical features. They were mostly edematous, hypertensive and anemic. They also had arthralgia, fever and oral ulcer. But patient with class II, III lupus nephritis presented with minimal clinical findings. They might had edema or arthralgia but no anemia, photosensitivity, alopecia or pericarditis. One-Way ANOVA test performed to observe the result of significance. Study finding shows that, the *f*-ratio value was 41.12977 and the *p*-value was 0.00001 ($p<0.001$). A study in Iran reported that most frequent presenting features were arthralgia (61.8%), edema (61.1%) and hypertension (61.1%).[20] The most frequent combination was arthralgia associated with edema and hypertension (37.5%). There was a significant correlation between edema and WHO classes (p= 0.004). Correlation between hypertension and WHO classification was also significant (p= 0.000).[20]

Our study design raises a number of important methodological issues, including patient selection, sample size and the prospective evaluation of association between histopathological findings of renal biopsy with clinical findings among patients with SLE, all of which may exert a powerful influence on the results. Most of the published studies lupus nephritis have focused on individual problems in isolation, such as clinical presentation, grading, or laboratory parameters. These studies have used a range of different designs; furthermore, methods of patient selection, diagnostic criteria, timing, and duration of follow-up vary considerably between studies, and therefore it is hardly surprising that the reported result of these studies also varied. But our study conducted in point of time and result correlated with other international, national study. An important strength of our study is place and duration. Teaching Hospital Bangladesh Medical College Hospital is a large tertiary care pioneer private hospital in country, situated in the metropolitan city of Dhaka. Huge number of patients admitted or transferred from rural areas of the country in this center with varied presentation and diverse clinical scenario.

However, this study was not without limitations. The limitations of the studies were as follows: Small sample size of the study population, it was a single center study. Only patients admitted in Bangladesh Medical College Hospital (BMCH) were taken for the study. So this will not reflect the overall picture of the country. A large scale study needs to be conducted to reach to a definitive conclusion. Study was conducted in a tertiary care hospital which may not represent primary or secondary center.

## Conclusion:

This study was carried out with an aim to observe the association of histopathological pattern of lupus nephritis with clinical findings. Lupus nephritis patients usually presented with edema, arthralgia, hypertension and malar rash. Most of the patients were in class IV and hypertension was the predominant feature. Early diagnosis and prompt institutional management with appropriate supportive therapy can make a favorable outcome in SLE patient. Although it is common that the persons with SLE are at high risk for future glomerular injury and still need to develop better measurement protocol to minimize and to prevent the negative consequences of this disease. The emphasis in SLE related glomerular disease prevention programs must be on early identification of patients at risk, and appropriate treatment by means of clinical, pathological and renal biopsy clarification as well.

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# Original Article

# Reasons of Blood Donor Deferral in a Selected Teaching Hospital in Dhaka City

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## Abstract

**Background:** Blood donor selection is a cornerstone of blood safety. The increasing demand of blood and blood components in the developing countries like Bangladesh reflects the need for mobilization of more voluntary blood donors to ensure a safe supply of blood and blood components. The deferral of blood donors is essential to protect the donors from the harms of blood donation or protection of recipient from TTIs (Transfusion Transmitted Infections).

**Objective:** To evaluate the reasons for blood donor deferral in order to facilitate proper donor education and reduce the number of deferment.

**Methods:** This cross-sectional, descriptive study was carried out in the department of transfusion medicine of a selected teaching hospital in Dhaka city. Data were collected from the records retrospectively and study subjects were donors for whole blood transfusion over a period of one year, from June 2016 to July 2017.

**Results:** Among the 5997 donors 427 were deferred and deferral rate was 7.1%. Majority 261(61.1%) were in the age group of 18 -30 years. Male donors were predominant (82.2%).Among the 427 deferred donors 24(5.6%) were permanent deferred and 403(94.4%) were temporary donors. The causes of permanent deferred were TB 8(33.3%), IDDM 5(20.8%), Cardiac diseases 4(16.7%), Rheumatoid diseases 3(12.5%), history of substance abuse 3(12.5%)etc. Among the 403(94.37%) temporary deferred donors, 48(11.9%) had visit in abroad, 38(9.4%) had history of regular medication, 36 (8.9%) had HTN,30(7.4%) infectious disease, 25(6.2%) had skin diseases, 24(5.9%) early donation, 22(5.4%) suffered from hepatitis A/E/D, 15(3.7%) had asthma,14(3.5%) tattooing, 13(3.2%) enteric fever,12(3.0%) history of vaccination,12(3.0%) under age that is less than 18 years,8(2.0%) menstruation, 7(1.7%) breast feeding etc.

**Conclusion:** Deferment from blood donation often decreases interest and also in number of donors. Evaluation of the profile of blood donors and increase awareness regarding common deferral reasons will help to increase the pool of voluntary donors and can increase the health status of the society.

**Keywords:** Blood donors, deferral, deferral reasons

## Introduction:

A blood donation occurs when a person voluntarily has blood drawn and used for transfusions and/or made into biopharmaceutical medications by a process called fractionation (separation of whole-blood components). Donation may be of whole blood (WB), or of specific components directly (the latter called apheresis).[1]

Blood safety has received major attention from the point of view of transfusion-transmitted infections, but it has been argued that the most important advancement in this area of medicine has been the collection of blood from non-remunerated repeat voluntary blood donors in the past 50 years instead of paid professional donors.[2,3] This process of blood donation involves voluntary and non-remunerated blood donors coming forward to donate blood willingly and the choice when and where to donate is dependent on blood donors' positive action.[4]

However, the transfusion services have a process of donor selection based on criteria of subjecting donors to a questionnaire, physical examination, and hemoglobin testing before blood donation, and only those who meet the requirements qualify as blood donors.[5,6]

Donor deferral criteria are designed to protect both the blood donor and the recipient from harm. The donor

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selection process results in deferral or rejection of potential blood donors who may not particularly like this feeling of being rejected and thus avoid returning for future donations.[7,8]

A major task for the blood banks is to take care of the regular donors. An important part of this strategy is to avoid donor deferrals, as donor deferral imposes a risk of "no-return" of the donor. The more the donor knows about reasons for deferral, the better will the chance be that the donor will not appear in the donation room in a state related to temporary deferral. [9]

Voluntary donation is a key issue in transfusion medicine. To ensure the safety of blood transfusions, careful donor selection is important. Although new approaches to blood safety have dramatically reduced the risks for infectious contamination of blood components, the quality and the availability of blood components depend on the willingness to donate and the reliability of the information given by the donors about their own health, including risk behavior. As donors who are deferred by the blood bank will be less motivated to return for donation, it is important to reduce the number of deferrals.[10]

The aims of the present study were to investigate the reasons for deferral of registered donors coming to the blood bank for donation, in order to identify areas of importance for donor education as these deferrals potentially could be avoided by better donor comprehension. Deferral related testing of donors is not included in this study as these deferrals are dependent on questionnaire or interview.[10]

## Materials and Methods:

This cross-sectional, descriptive study was carried out in the department of transfusion medicine of a selected teaching hospital in Dhaka city. Data were analyzed retrospectively for whole blood donations over a period of one year, from June 2016 to July 2017. Donors presenting at indoor as well as outdoor locations were included in the study. Standard Operating Procedures based on national guidelines were used for donor selection and deferral. Predesigned data sheets of donors were filled by blood donors on the basis of a detailed clinical history, which included information about jaundice, malaria, ulcers, diabetes, syphilis, tuberculosis, history of hepatitis B and C infection, rheumatic fever, cardiac or renal disease, convulsion or fainting spells, loss of weight, previous blood donations, allergy, serious illness, surgery, blood transfusion, immunization and a history of pregnancy in the case of females. A brief physical examination, especially for signs of anemia, jaundice and fever, blood pressure, pulse, temperature, respiratory rate, weight and any visible abnormality, was carried out.

Briefly, the cutoff for hemoglobin (Hb) was 12 gm/dl by the finger prick method; and all female and doubtful values for male donors were confirmed for correct Hb by Hemocue Hb 201+ (HemoCue AB, Angelholm, Sweden). Using these two time tested methods for Hb estimation together as complimentary tests has proved to be a cost-effective and sensitive screening test.

Donors with systolic blood pressure between 120 and 140 mmHg diastolic blood pressure between 60 and 90 mmHg alone were accepted for blood donation; an average of three measurements of B.P. was taken for those not falling within this range for systolic and/or diastolic B.P.

In general Standard operating procedures (SOPs) based on the National Blood Donor Policy (2011) developed by Safe Blood Transfusion Programme were used for donor selection and deferral. Based on their history and physical examination findings, all blood donors were classified into those fit for donation or deferred. Individuals who did not meet the donor selection criteria based on the assessment of medical history and risk for TTIs, resulting in temporary or permanent deferral, were defined as follows;

**Temporary deferral:** Prospective donor unable to donate blood for a limited period of time and can return for future blood donations after the defined deferral period.

**Permanent deferral:** A designation applied to a blood donor who for one or a variety of reasons will never be allowed to donate blood.

**Voluntary donor**: A person who gives blood, plasma or a component freely and voluntarily without receiving payment in the form of money or a substitute for money, but only for an internally generated sense of altruism or community responsibility.

**Family or replacement donors**: A friend or family member of the recipient who donates blood to replace the stored blood used for the blood transfusion of the recipient, ensuring a consistent supply of the blood in the blood bank.

Records of all pre-donations were analyzed to quantify the deferral rate and reasons. Donors deferred were differentiated according to age and whether deferral was temporary or permanent. The statistical package SPSS-17 was used to analyze the data. Frequency and percentages were computed to determine the reasons for donor deferral.

## Results:

**Table 1:** Distribution of the donors by Socio demographic characteristics

| Age | Deferred | Selected | p value |
|---|---|---|---|
| 18 -30 years | 261(61.1% | 4066(73.0%) | <0.005 |
| 31-40 years | 100(23.4%) | 1195(21.5%) | |
| 41-50 years50- | 55(12.9%) | 288(5.2%) | |
| 60 years | 11(2.6%) | 21(.4%) | |
| **Sex** | | | |
| Male | 351(82.2%) | 5198(93.3%) | <0.005 |
| Female | 76(17.8%) | 372(6.7%) | |
| **Marital status** | | | |
| Married | 215(50.4%) | 2414(43.3%) | <0.005 |
| Unmarried | 212(49.6%) | 3156(56.7%) | |
| **Education** | | | |
| Under graduate | 152(35.6%) | 1930(34.6%) | >0.05 |
| Graduate | 167(39.1%) | 2810(50.4%) | |
| Master and above | 85(19.9%) | 423(7.6%) | |
| Illiterate | 23(5.4%) | 407(7.3%) | |
| **History of Blood donation** | | | |
| Yes | 218(51.1%) | 2667(47.9%) | >0.05 |
| No | 209(48.9%) | 2903(52.1%) | |
| Total | 427(100.0%) | 5570(100.0%) | |

Table 1 shows that among the 5997 donors 427 were deferred with deferral rate of 7.1%. Among the deferred donors majority 261(61.1%) were in the age group of 18-30 years. Among the deferred donors male were 351(82.2%) and female were female 76(17.8%); married and unmarried were almost equal, 215(50.4%) and 212(49.6%) respectively; majority were graduate 167(39.1%).

**Table 2:** Distribution of the donors by blood group

| | Selection | | |
|---|---|---|---|
| **Blood group** | **Deferred** | **Selected** | **p value** |
| A +ve | 71(16.6%) | 1265(22.7%) | >0.05 |
| B +ve | 181(42.4%) | 1990(35.7%) | |
| O +ve | 122(28.6%) | 1842(33.1%) | |
| AB +ve | 37(8.7%) | 412(7.4%) | |
| A –ve | 4(0.9%) | 10(0.2%) | |
| B –ve | 6(1.4%) | 6(0.1%) | |
| O –ve | 5(1.2%) | 32(0.6%) | |
| AB –ve | 1(0.2%) | 13(0.2%) | |
| Total | 427(100.0%) | 5570(100.0%) | |

According to ABO group and Rh Factor B+ve were the most common in deferred 181(42.4%) and also in selected 1990(35.7%), then O+ve 122(28.6%) and1842(33.1%) followed by AB+ve 37(8.7%) and 412(7.4%) as shown in Table 2.

**Table 3:** Distribution of the donors by Types of deferral

| Types of deferral | Frequency | Percentage |
|---|---|---|
| Permanent | 24 | 5.62 |
| Temporary | 403 | 94.37 |
| Total | 427 | 100.0% |

Among the 427 deferred donors 24(5.62%) were permanent deferred and 403(94.37%) were temporary donors (Table 3).

**Table 4:** Distribution of the donors by Causes of Permanent deferral

| Causes of Permanent deferral | Responses | |
|---|---|---|
| | Frequency(n=24) | Percent of Cases |
| IDDM | 5 | 20.8% |
| Cardiac diseases | 4 | 16.7% |
| Hepatitis B/C | 1 | 4.2% |
| TB | 8 | 33.3% |
| Rheumatoid diseases | 3 | 12.5% |
| History of substance abuse | 3 | 12.5% |

** multiple response

Table 4 shows that the causes of permanent deferred were mostly due to TB 8(33.3%) followed by IDDM 5(20.8%), Cardiac diseases 4(16.7%), Rheumatoid diseases 3(12.5%), history of substance abuse 3(12.5%) etc.

**Table 5:** Distribution of the donors by Causes of temporary deferral

| Causes of Temporery deferral | Responses | |
|---|---|---|
| | Frequency(n=403) | Percent of Cases |
| HTN | 36 | 8.9% |
| NIDDM | 6 | 1.5% |
| Asthma | 15 | 3.7% |
| Hepatitis A/E/D | 22 | 5.4% |
| Malaria | 5 | 1.2% |
| Venereal diseases | 2 | 0.5% |
| Skin diseases | 25 | 6.2% |
| Piles | 4 | 1.0% |
| Peptic ulcer disease | 1 | 0.2% |
| Enteric fever | 13 | 3.2% |
| Blood Dysentery | 3 | 0.7% |
| Infectious disease | 30 | 7.4% |
| History of Abortion | 2 | 0.5% |
| Breastfeeding | 7 | 1.7% |
| Menstruation | 8 | 2.0% |
| Operation last 6 mns | 3 | 0.7% |
| History of tooth extraction | 4 | 1.0% |
| History of Vaccination | 12 | 3.0% |
| History of blood Transfusion | 2 | 0.5% |
| History of Aspirin taking-last 7 days | 1 | 0.2% |
| History of regular medication | 38 | 9.4% |
| Tattooing | 14 | 3.5% |
| Early donation | 24 | 5.9% |
| Under age | 12 | 3.0% |
| Weight <50 kg | 32 | 7.5% |
| Hb % below 12 mg/dl | 55 | 12.9% |
| Visit abroad | 48 | 11.9% |

** Multiple responses

In Table 5 it is shown that among the 403(94.37%) temporary deferred donors 348(86.1%) had meal in last 2 hours, 48(11.9%) had visit in abroad, 38(9.4%) had history of regular medication,36(8.9%) had HTN,30(7.4%) infectious disease, 25(6.2%) had skin diseases, 24(5.9%) early donation,22(5.4%) suffered from hepatitis A/E/D, 15(3.7%) had asthma,14(3.5%) tattooing, 13(3.2%) enteric fever,12(3.0%) history of vaccination,12(3.0%) under age that is less than 18 years,8(2.0%) menstruation, 7(1.7%) breastfeeding etc.

## Discussion:

Donor counseling and screening through questionnaire before donation is an important process not only to ensure blood safety but also to recruit and retain regular voluntary non remunerated donors. The deferred donors are informed about the reason of deferral and counseled accordingly.[11] Knowledge of deferral incidence and causes in a particular region helps in deciding the magnitude and direction of blood donor recruitment efforts. This knowledge also helps in calculating the eligible and potential blood donor pool. The eligible donor pool may drastically vary from the potential donor pool which is usually calculated on the basis of age alone (population between 18 and 60 years of age).[12] The donors below the age of 18 years and above 60 years are not allowed to donate. However, there is relaxation in case of regular donors and they can donate up to 65 years.[13]

This fact was highlighted by William Riley and colleagues in their study where they showed that the conventional method of determining eligible donors, using age alone as the criteria, overestimated eligible donor prevalence (calculated using deferral incidence) by approximately 59 percent.[12]

In this study among the 5997 donors 12 donors (3%) were rejected temporarily due to under age means below the age of 18 (Table 5) The donor deferral rate has been reported from 5.19% to >30% in different countries.[13,14,15,16,17,18,19,20]

The lowest rejection rate was 4% reported by Talonic[21] in Papua New Guinea while Chaudhry[22], Lim[23], and Ranveet[24] reported 8%-15% deferral rates in their studies.In contrast another study revealed 30.9% deferral rate. The deferral rate was significantly higher among women and married people.[25]

In this study according to blood group and Rh Factor B+ve were the most common in deferred 181(42.4%) and also in selected 1990(35.7%), then O+ve 122(28.6%) and 1842(33.1%), followed by AB+ve 37(8.7%) and 412(7.4%) as shown in Table 2. Almost similar results were found in a study where the ABO blood groups were present as B (35.15%), followed by O (34.73%), A (22.09%), and AB (8.03%) in blood donors while in Rh system, (96.46%) donors were Rh+ve and (3.54%) donors were Rh−ve.[26]

In a study, 302 (3.55 %) out of total 8767 registered prospective blood donors were found unfit to donate for various reasons; the majority (82.05%, n =257) were deferred for temporary reasons, and a smaller subset (17.66 %, n =55) were permanently deferred. Most of the donors were males (94.01 %); women accounted for only 6.0 % of the donors. Analysis of blood donor deferral characteristics in a Blood Bank at A Tertiary Care Hospital attached to Medical College in Gujarat reveals that 17.66 % of donors were deferred for permanent reasons [27] and Usman et al (2016)[28] reported a permanent deferral rate of 6.1% and Arslan (2007) reported a rate of 10%.[29] In our study among 5997 donors, total 427 (7.1%) were deferred where permanent deferral was 24 (5.62%) and temporary was 403 (94.37%) (Table:3).

In another study shown that women had a very high deferral rate in comparison to men reflecting the poor nutritional status of female in Manipal[27], and Delhi[13]. As reiterated in the national health policy of achieving 100% voluntary donation, our blood bank received 88% of its donors as voluntary donors in comparison to 12% replacement donors, which is way above the national average of 39.3%[13]. In our study according to sex male were more than the female. Among the deferred donors male were 351(82.2%) and female were female 76(17.8%). But in case of selected donors only 372(6.7%) were female (Table 1).

The one of the most common causes of temporary deferral in our study was hypertension 8.9% (Table 5). Similar to a study by De Lorenzo Oliveria et al (2009).[30] Hypertension was noted as common cause of deferral in a similar study by Bahadur *et al*.[13,31,32] It was surprising that hypertension, along with cardiac problems, was roughly equally distributed in various age groups. In younger age groups, this might be due to apprehension and anxiety for donation, induced by fear of phlebotomy or fear of the sight of blood.[33] Hypertension leads to permanent deferral of a substantial number of potential blood donors in a study by Bahadur *et al*. was due to nervousness and anxiety of the first-time donors.[13]

The another most common cause for deferral was low hemoglobin (42.02 %) similar to that reported by Bahadur and colleague (2009)[13] (32.9%) and Custer et al (2004)[14] (60% of temporary deferrals) and Halperin et al (1998)[34] (46%). In this study also low haemoglobin count was the common cause of donor deferral where among 427 deferred donors 55(12.9%) were deferred for low hemoglobin count below 12 mg/dl (Table 5). In India, Bahadur and colleagues[13] in their study with predominantly replacement donors (99.4%) found low Hb as the most common cause of deferral (32.9%). Similarly, in another Indian study by Chaudhary and colleagues[22] low Hb (18.6%) were respectively the two most common reasons for the deferral.

Low hemoglobin was the commonest cause of deferral in a similar study conducted by Antwi-Baffour et al.[35] The minimum cut-off hemoglobin level for blood donation is >12.5 gm% irrespective of sex. The second most common cause for deferral was body weight below 50 Kilograms 277 (15.48%), followed by under age 151 (7.79%) in a hospital of western India.[33]

Like most of other studies done in the past, [13,14,34,36,37,38] the most common reason for deferral in whole blood donor population was low hemoglobin and nearly 56% of total deferrals were because of this. Nearly two third of these anemic donors were females highlighting the prevailing anemia in general population among females. Also, odds ratio indicated very high probability of deferral in females as compared to males due mainly to low Hb. There was no difference in deferral in voluntary and replacement donors due to low Hb. The most common cause of deferral in another study was anemia (41%). This is in agreement with earlier studies.[39,40] The majority of these were females. As reported in other studies, up to 95% of the deferrals for anemia occur in females.[34,41] The blood donors deferred due to anemia are much less likely to reappear for future donations than donors who are not deferred. A study reported that only 21% first-time donors having anemia came back to donate within 3 years while 70% of those not deferred returned. Similarly, only 64% of repeat donors returned within 3 years after low Hb deferral while 91% of those not deferred returned.[42]

Indian studies from Chandigarh[43] and Lucknow[44] report jaundice as the most common cause of deferral where in our study it was 22(5.4%) as shown in Table 5. In a study by Halperin *et al*.[34] the three most common causes of temporary deferral were low hemoglobin, cold/sore throat and fever but in our study about 7.4%(30) donor were deferred due to various infectious cause like fever, chest infection, sore throat, etc.

Body weight is related to poor health status of the general population and poor nutrition being common in low socio economic groups. Under-aged potential donors were unaware of basic requirements for blood donation, i.e. age, weight and hemoglobin percentage, indicating the importance of public awareness and education for successful voluntary blood donation.[33] The second and third most common reasons in a study were low weight (26.6%) and history of jaundice/ hepatitis (8.1%). Similarly in another Indian study by Chaudhary and colleagues[22] low weight (32.3%) and low Hb (18.6%) were respectively the two most common reasons for the deferral. In another study the second most common cause of deferral was low weight, which accounted for 11.28 % of total deferrals.[27] Like all other study underweight was also another most common cause of deferral in our study. Among 427 donors 32(7.5%) donors were deferred for under weight (below 50KG) as seen in Table 5.

## Conclusion:

The deferral of donors due to any reason has a very negative impact for the donor as deferring prospective donors often leaves them with negative feelings about themselves as well as the blood donation process which may potentially decreases the chances of return of these donor for future donation. It is also necessary to follow strict donor selection criteria to make blood donation safe and win the trust of future donors. The present study on donor deferral rate and reasons among the blood donors concludes that, the males are predominant donors and majority are below the age of 30years. Temporary deferral is much more than permanent deferral and mostly due to less hemoglobin, various active infection and hypertension.The main cause of permanent deferral was previous history of Tuberculosis and IDDM.

It is high time to take stock of the present and future precious blood units lost due to these deferrals. Awareness among the blood donors should be regenerate to keep them

safe and healthy for not only future blood donation but also to make a healthy population.

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# Review Article

# Prognostic Factors of Ovarian Cancer in Recent Research

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## Abstract

Survival following ovarian cancer is influenced by many factors. In this article, we have summarised important prognostic factors based on recently published articles on survival following ovarian cancer. Comparing with previous reviews several additional important prognostic factors have been identified in this research, including surgery, presence or absence of ascites, ALP and albumin levels. There are also a number of prognostic factors included in the previous review, such as bulky disease at diagnosis, have not been considered in the recent articles as observed in our study.

**Keywords:** Ovarian cancer; Prognostic factors; Survival

## Introduction:

Ovarian cancer is the leading cause of gynaecological cancer deaths in many countries, including United States, United Kingdom and Australia.[1,2] An estimated 22,240 new cases of ovarian cancer were diagnosed and 14,230 women were expected to die from ovarian cancer in the United States in 2013. According to a recent report published by cancer research UK[3], in 2014, there were 7,378 new cases of ovarian cancer diagnosed in the UK and 4,128 women died of this disease. In Australia, each year around 1300 women are diagnosed with ovarian cancer and more than 800 women die from the disease.[4] In general, women with ovarian cancer have poor prognosis with short survival. Winter III et al.[5] estimated an overall median survival of 29 months among patients with advanced ovarian cancer. The prognosis is worse when the cancer is diagnosed at a late stage, which is quite common for ovarian cancer as there are not many clear symptoms for the disease until tumour has metastasized. Therefore, it is very important to investigate and identify the prognostic factors of survival following a diagnosis of ovarian cancer.

There have been a large number of studies on ovarian cancer over last few decades. Many of them were aimed to predict or estimate survival rate and identify the prognostic factors associated with the survival for people with ovarian cancer, using various methods of survival analysis, such as the Cox proportional hazards model. A review of the prognostic factors of ovarian cancer was published in 1995[6] and another in 2014.[7] The earlier review was more informative and each of the prognostic factors considered was evaluated and categorised in some meaningful labels. However, the latter review by Ezzati et al.[7], which did not mention any previous review, only listed and described commonly used prognostic factors and no labelling was used in their review. Our review article would remove the gap of previous reviews and would be more interesting and add value to the current knowledge of prognostic factors of ovarian cancer.

During the last few decades many more studies on survival following ovarian cancer were carried out and published. This must have enhanced the knowledge and understanding of the prognostic factors of survival following ovarian cancer. Moreover, technological improvement over those years might have resulted in better use or modification of the treatment for the disease or possibly new treatments or treatment schemes. Understanding the prognostic factors of ovarian cancer can help identify subgroups of patients according to their prognosis and thus enable doctors to apply appropriate treatment. Therefore, there is need for a review of recent studies of the prognostic factors associated with survival following ovarian cancer, to understand changes in the last few decades, if any, in both the prognostic factors of and treatment for ovarian cancer.

## Materials and Methods:

In this article we review scientific publications on survival following ovarian cancer between 1995 and 2014, focusing on the prognostic factors of ovarian cancer. We have considered the recent studies as well as review articles of the prognostic factors associated with survival following ovarian cancer. Those articles were obtained using Google search engine. We have used different key words while google searching for finding the articles, such as prognostic factors of ovarian cancer, ovarian cancer survival, survival analysis of ovarian cancer patients etc. Therefore, our review paper would consider articles, both original and review, that cover either prognostic factors or survival analysis of ovarian cancer patients reflecting the effects of prognostic factors taken into account in them.

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## Results and Discussion:

Ovarian cancer is not a homogeneous disease but rather a group of diseases, each with different morphology and biologic behaviour. It is classified into various types and stages, which may be associated with differing prognoses. Besides types and stages, many other factors may be associated with the prognosis of ovarian cancer. Some of these factors have been considered and/or identified as prognostic variables in the literature. Brinkhuis et al.[6] have summarised the prognostic variables/factors based on some of ovarian cancer studies published before 1995. The results from the present review of the prognostic factors considered in the early review are presented in the right column of Table 1.

**Table 1:** Prognostic value by factor on survival following ovarian cancer

| | Prognostic value | |
|---|---|---|
| **Variable** | ***Brinkhuis et al.'s[6] review*** | ***This review*** |
| ***Clinical factors*** | | |
| FIGO stage | Proven | Proven |
| Residual disease status | Proven | Proven |
| Performance status | Proven but subjective | Proven |
| Chemotherapy | Proven | Proven |
| Physician's speciality | Proven | Proven |
| ***Other factors*** | | |
| Age | Proven but biased | Proven |
| Race | Proven but biased | Proven |
| CA 125 | Conflicting | Conflicting |
| Histologic type | Conflicting | Conflicting |
| Grade | Proven but subjective | Proven |
| Oestrogen receptor | Conflicting | Conflicting |
| Progesterone receptor | Conflicting | Conflicting |
| c-erb-$B_2$ | Conflicting | Potential |
| EGFR | Proven | Potential |
| P53 | Conflicting | Conflicting |
| Mitotic activity index | Proven | Proven |
| Nuclear grade | Proven | Proven |
| Volume percentage epithelium | Conflicting | Proven |
| Morphometric groups | Conflicting | Proven |

Prognostic values of different prognostic factors were defined by Brinkhuis et al.[6] Those values are 'proven', 'conflicting' and 'indefinite'. If factors are found significant in all articles reviewed they are labelled as 'proven', the term 'conflicting' indicates any factors with contradictory findings across articles reviewed, and 'indefinite' is for factors with inconclusive results. In addition, we have defined another prognostic value 'potential' for factors reported with marginal effects. Note that two of the prognostic values used in Brinkhuis et al.'s[6] review, 'proven, but subjective' and 'proven, but biased', have not been used in the present review considering that they are rather subjective. Moreover, in the review by Ezzati et al.[7], there is no mention of such prognostic value, so their findings could not be compared.

As shown in Table 1, prognostic values of International Federation of Gynaecology and Obstetrics (FIGO) stage, residual disease status, chemotherapy, physician's speciality, mitotic activity index and mean nuclear area for survival following ovarian cancer are considered 'proven' in both Brinkhuis et al.'s[6] review of early studies and this review of more recent studies. The results on the associations of performance status, age, race, grade, volume percentage epithelium and morphometric groups with the survival were not conclusive or consistent among studies included in the early review, but have been ascertained, i.e., 'proven', in the present review. Epidermal growth factor receptor (EGFR) was a 'proven' factor in Brinkhuis et al.'s[6] review but not in the current review.

Several factors, such as CA 125 (Cancer Antigen 125), histologic type and p53, have the prognostic value, 'conflicting', in both early and this review, and thus may need further investigation. Note that a number of factors included in the early studies, including bulky disease at diagnosis, macrophage-colony stimulating factor (M-CSF), cancer associated serum antigen (CASA), Sialyl-TN, Psammoma bodies, Androgen receptor, platelet-derived growth factor receptor (PDGFR), lung resistance protein (LRP), advanced carcinoma of the ovary prognostic score (ACOPS) and deoxyribonucleic acid (DNA) ploidy, were not considered in the recent studies reviewed. Of them only bulky disease at diagnosis and ACOPS were identified as having important prognostic value for the survival following ovarian cancer in the early review.

FIGO stage is widely used in ovarian cancer research, such as studies of Obermair et al.[8], Kotsopoulos et al.[9], Chan et al.[10] etc. Tingulstad et al.[11] and Clark et al.[12] suggested that FIGO stage is a significant prognostic factor for ovarian cancer. There are other methods for staging ovarian cancer, such as Surveillance, Epidemiology, and End Results (SEER) stage,[13] although fewer studies have adopted this. SEER stage is classified as localised, regional and distant. Women with localized disease, who had undergone surgery, have the best survival.[13,14]

Amount of residual tumour (i.e., residual disease) after surgery, i.e., debulking procedure, was identified as significant prognostic factor in Polterauer et al.[15], Tingulstad et al.[11], Chi et al.[16], etc. In a study of patients with advanced ovarian cancer, Colombo et al.[17] found that patients with no residual disease after the debulking procedure had experienced a better prognosis with a greater 5-year survival rate.

They also reported that survival of patients with ovarian cancer at advanced stage was mainly influenced by three

factors: the biology and chemo-sensitivity of the tumour, the size of the residual disease as well as the extent of the disease at the time of diagnosis.

Clark et al.[12] suggested that performance status is an important prognostic factor for overall survival of ovarian cancer patients. This was supported by a few other studies (e.g., Colombo et al.[17]). According to Barnholtz-Sloan et al.[13], patients who failed to undergo surgery were often those who were in the advance stage of the disease with poor performance status and medical comorbidities, and thus might be too weak for the surgery. Only more recently, patients in such poor condition may be offered to first receive chemotherapy treatment, and then undergo a surgery followed by further chemotherapy.

Chemotherapy treatment plays an important role in the prognosis of ovarian cancer patients. The effectiveness of surgery may well depend on whether the chemotherapy treatment is received before debulking. According to Colombo et al.[17], the result of surgery was optimal for 63% of the patients who received debulking surgery without prior chemotherapy treatment, whereas it rose to 84% among patients who received their debulking after a prior chemotherapy. The surgeon's specialty was also demonstrated as a significant prognostic factor by several studies (e.g., Vernooij et al.[18]; Kumpulainen et al.[19]; Olaitan et al.[20]).

Age at diagnosis is found to be a significant prognostic factor for ovarian cancer patients in a number of studies, such as Chan et al.[10], Tingulstad et al.[11] and Clark et al.[12]. Older women (age > 60) experienced worse prognosis with a short survival following the diagnosis of ovarian cancer.[13,17]

In terms of race, two-year relative survival increased significantly over time for Caucasian women with ovarian cancer. The African American women experienced the worst prognosis with a five-year relative survival of all races.[10,13]

CA 125 was discovered by Robert Bast in early 1980s. The plausibility of CA 125 as a prognostic factor for ovarian cancer disease was evaluated in some studies. Markmann et al.[21] found that the level of CA 125 correlated with overall survival. According to them, levels around 100 U/l are indicative of a bad prognosis. However, the levels of CA 125 were not found to be sufficient in predicting the possibility of performing optimal surgery in the study of Chi et al.[22] Nowadays, CA 125 is used to monitor the response to chemotherapy.[23]

Among different histologic types of tumour, women with mucinous and endometriod tumours had better 5-year survival over the other types.[13] It was also suggested as an important prognostic factor in several studies, such as Clark et al.[12]

Ahmed et al.[24] found grade an important prognostic factor. It was mentioned as a standard prognostic variable for ovarian cancer by Eisenhauer et al.[25] This was also found significant in the study by Seiden.[26]

The results on the prognostic effects of oestrogen receptor (ER) and progesterone receptor (PR) are rather inconsistent. Liu et al.[27] found that these two factors were not associated with survival following ovarian cancer. However, Hogdall et al.[28] identified the prognostic value of ER and PR. According to Geisler et al.[29], PR does not affect survival, but low level of ER (less or equal to 10 fmol/mg) may be indicative of a better prognosis. In a more recent research carried out by Sieh et al.[30], it is claimed that PR and ER are prognostic biomarkers for endometrioid and high-grade serous ovarian cancers.

Based on a meta-analysis, Crijns et al.[31] found the therapeutic potentiality of the putative prognostic molecular biological factors, such as human epidermal growth factor receptor 2 (HER-2)/neu (c-erb$B_2$), EGFR, and p53.

The mitotic activity index was found in the study by Shimizu et al.[32] an important prognostic variable for stage I/II and stage III/IV ovarian cancer. It was associated with the survival following ovarian cancer for most combinations of histologic type and stage.

The prognostic factor, nuclear grade, is determined by the variation in nuclear size and shape, chromatin texture and some other elements of the tumour. Nuclear grade was found significantly associated with survival of ovarian cancer patients.[32,33] Nuclear irregularity is also positively associated with both death and disease recurrence according to Liu et al.[34]

Katsoulis et al.[33] identified another pathological factor, volume percentage epithelium (VPE), as a significant prognostic factor, and suggested that ovarian cancer patients with low values of VPE seemed to have a better survival prospects. Liu et al.[34] indicated that morphometric groups might be useful in predicting outcome in patients with early stage ovarian clear cell adenocarcinoma. Most of the morphometric parameters were significantly associated with survival according to Katsoulis et al.[33]

There are a number of additional factors investigated in the recent studies between 1995 and 2014, which were included in the present review but not considered in the early studies reviewed. The results on these factors are presented in Table 2. Surgery, presence or absence of ascites, Alkaline phosphatise (ALP) and albumin levels have prognostic value 'proven', while marital status and GST-pi have 'potential' prognostic value for survival following ovarian cancer. The results about the effects of height, weight and BMI on the survival are rather mixed, ie, 'conflicting', which need further investigations in future studies.

Clark et al.[12] found that surgery, ie, debulking of the tumour, is an important prognostic factor. A significantly better 5-year survival was evident for ovarian cancer patients who had the surgery. Chan et al.[10] found that surgery was an independent prognostic factor for improved survival, and

the study by Colombo et al.[17] confirmed the importance of surgery in the prognosis of advanced ovarian cancer.

Married women experienced better 2 and 5-year survival than women who had never married.[13] Besides many other reasons, familial advantages might be behind this better survival.

Kotsopoulos et al.[9] examined the relationship between adult height, weight or BMI and ovarian cancer specific mortality. Findings of this study did not support a role of height, weight or BMI in the prognosis of ovarian cancer. However, the study of Rodriguez et al.[35], which considered only postmenopausal women, identified a positive association between height and ovarian cancer mortality. They also found that overweight and obesity appeared to be associated with increased risk of ovarian cancer mortality for women who had never used postmenopausal estrogen therapy. The results of these two studies are clearly contradictory, and this kind of conflicting results was also reported in the study of Protani et al.[36].

**Table 2:** Additional factors considered in recent research

| Variable | Prognostic value |
|---|---|
| Surgery | Proven |
| Marital status | Potential |
| Height | Conflicting |
| Weight | Conflicting |
| BMI | Conflicting |
| ALP | Proven |
| Albumin | Proven |
| Presence or absence of ascites | Proven |
| GST-pi | Potential |

Clark et al.[12] found ALP and Albumin significant prognostic factors for survival following ovarian cancer. The factor, presence or absence of ascites, was also shown statistically significant in the study, as well as in the studies by Chi et al.[16], Colombo et al.[17] and Anuradha et al.[37]. The factor Glutathione-S-transferase-pi (GST-pi) was identified as a potential prognostic factor by Crijns et al.[31]

In summary, important prognostic factors of ovarian cancer identified in this review include FIGO stage, residual disease, performance status, age, surgeon's speciality, grade, CA125, histologic type, mitotic activity index and nuclear grade. These factors were also found as important in the previous reviews. Several additional factors, including surgery, ALP, albumin and presence or absence of ascites, have also played important role in the prognosis of survival following ovarian cancer as revealed in the current review.

## Conclusion:

We have summarized different prognostic factors of survival following ovarian cancer and many important prognostic factors suggested in the early review have been supported by this review. Several other important prognostic factors, surgery, presence or absence of ascites, ALP and albumin, which were not considered in earlier studies, have been identified in the present review.

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# Case Report

# Cervico-deltopectoral Flap- for Single Stage Reconstruction of Large Facial Defects: A Case Report

Siddiky S[a], Siddiky S[b]

## Abstract

Cutaneous defects of the head and neck, no matter for what reason, have to be given a lot of thought before reconstruction. The aesthetic factor is very important in considering the outcome of the procedure, where possible; especially if the patient is young. If the lesion is big then primary closure is often not possible. In that case the options are serial excision, these procedures require two or more sittings; and therefore, the patient has to come back for follow up procedures. For large facial defects, adding a cervical extension to the conventional deltopectoral flap, makes the reconstruction easier- as it gives a bigger flap; and more importantly the procedure can be completed in one sitting. We report here a case of giant epidermal verrucous naevus on the left cheek, treated by total excision and complete resurfacing using a cervicodeltopectoral flap in a single sitting.

**Keywords**: Cervicodeltopectoral flap, Reconstruction, Facial defect.

## Introduction:

The deltopectoral flap was first described by Aymard in 1917, but Bakamjian made it popular by using it to reconstruct various defects in the head-neck area. It was also known as the Bakamjian flap.[1] Instead the deltopectoral flap is being used for various reconstructive procedures. As we know the deltopectoral flap is based on a dual blood supply arising from the medially based second and third perforators of the internal mammary artery and laterally based cutaneous branches of the thoracoacromial, subscapular, and circumflex humeral vessels.[2] The Cervicodeltopectoral (CDP) flap is also based on the branches of the internal mammary artery but it is not limited by the clavicle and the deltoid muscle.

## Case Presentation:

A child ten years of age, presented at Cosmetic Surgery Centre Ltd. with a giant epidermal verrucous naevus on the left cheek (Fig-1). It was 7cm in diameter and occupied almost the whole of left cheek. There were also evidence of small isolated cutaneous excrescences on the nose and left ear. Appropriate preoperative workup was done and the patient was subjected to excision followed by resurfacing with CDP flap. Under GA and preoperative marking wide local excision of the cheek lesion was done. A CDP flap was then constructed based on the perforators of internal thoracic arteries (Fig-2). After careful hemostasis the flap was advanced upward and forward to resurface the cheek defect (Fig-3). Repair was performed by a single layer of interrupted 4/0 and 5/0 prolene stitches. In the postoperative period the patient received a course of antibiotic and analgesic; and daily check was done to assess flap vascularity. Stitches were removed on 7th and 12th POD. Photographs were taken at 1month, 6 months, 1 year and 4 years (Fig-4) after the surgery.

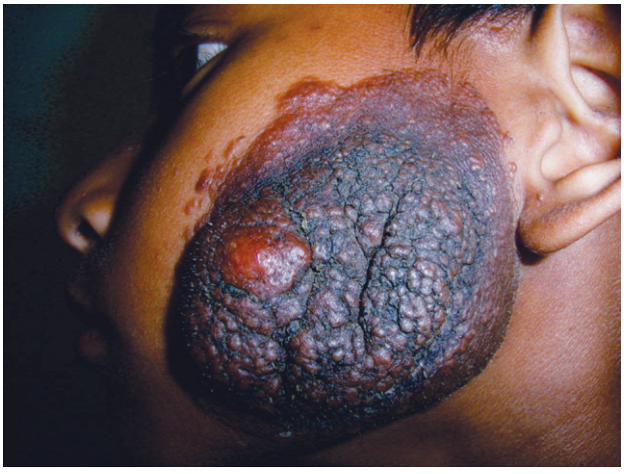

**Fig. 1:** A giant epidermal verrucous naevus on the left cheek

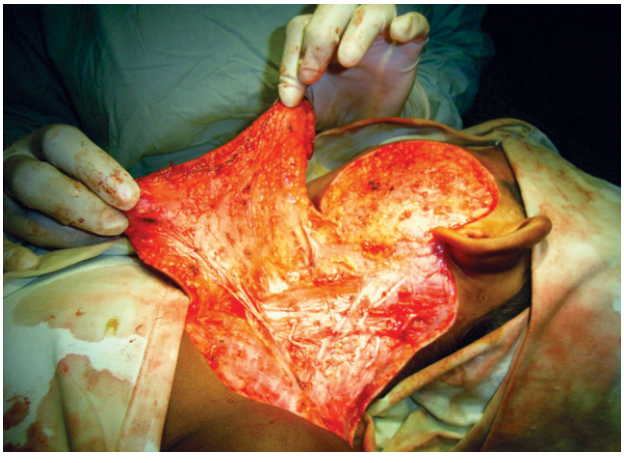

**Figure 2:** A CDP flap constructed based on the perforators of internal thoracic arteries.m: 8.8mg/dl & Electrolytes: Na:

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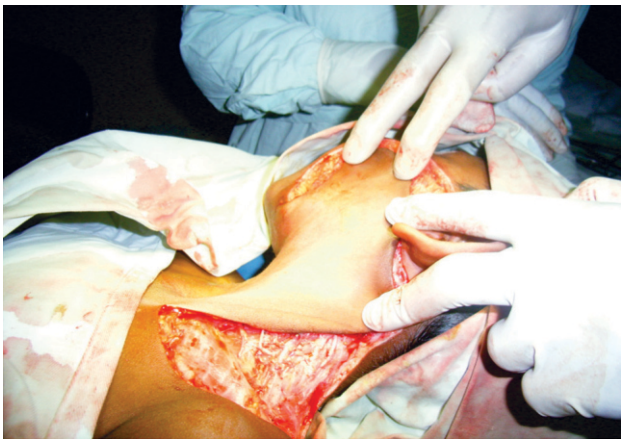

**Figure 3:** After careful hemostasis the flap was advanced upward and forward to resurface the cheek defect

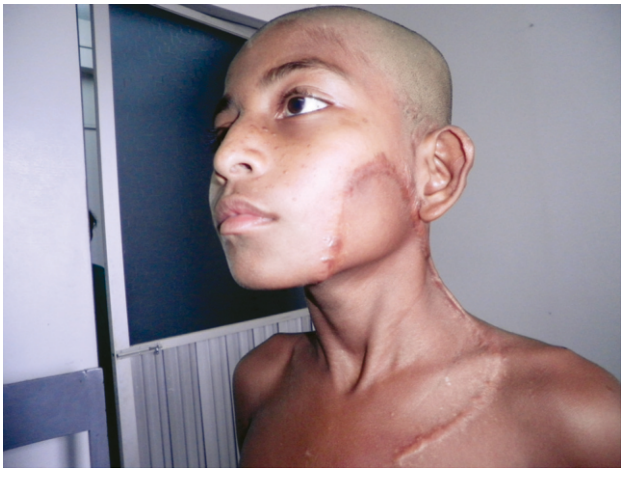

**Figure 4.** Four years after the operation.

## Discussion:

Large defects on the face are very difficult to treat as a lot of consideration has to be given to the aesthetic outcome of the procedure, especially if the patient is young. Cervicodeltopectoral flap is a suitable flap that is big enough and has the closest texture and color match to the adjacent skin. This makes it a more acceptable flap from aesthetic point of view. More importantly there is no need for second stage surgery as in the case of deltopectoral flap.

Usually nasolabial flap, forehead flap or deltopectoral flaps or tissue expanders are used for resurfacing of defects on the face. But their drawbacks include limited size and also the need for more than one step to complete the surgery. The need for more than one sitting can sometimes become frustrating for the patient.

Although cervicofacial rotation flaps have been well described for reconstruction of large cheek defects, they generally do not provide enough skin for single-stage, single flap reconstruction of large through-and-through defects of the cheek.[3,4] Inferior extension of the standard cervicofacial flap into a CDP flap enhances flap reliability by providing it with a direct arterial axial blood supply. In addition, the CDP flap increases tissue availability to allow for the turning in of the superior portion of the flap, thus reconstructing the inner and outer aspects of the cheek, if required. Wallis and Donald described the use of a pectoral extension to the cervicofacial flap and noted an increase in available tissue for facial reconstruction. [5] The use of a single flap and the quick resurfacing of big cervical defects are important advantages to the use of this flap.

The CDP flap appears to be quite reliable in terms of its vascularity. In one series of 18 patients, there was no evidence of flap loss in any one.[6] This reliability is partly attributable to the axial blood supply, but also to dermal-subdermal plexus interconnections from any remaining medial cervical attachments of the flap. Although a beneficial delay phenomenon in deltopectoral flaps may be documented experimentally with xenon blood flow studies substantial clinical evidence of its routine use is lacking.[7,8] The reliability of the CDP flap suggests that delay of this flap is also unnecessary.

## Conclusion:

We found the CDP flap to be a very convenient and reliable way of resurfacing complex cutaneous defects of the face and neck. It is simple and reliable in terms of skin color and texture match, and also is a good alternative for 2-stage operations. It should be used more commonly for resurfacing of facial defects.

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# Case Report

# Primary Retroperitoneal Mucinous Cystadenoma in a Post-hysterectomy Patient: A Case Report

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## Abstract

Primary retroperitoneal mucinous cystadenomas (RMC) are very rare, even though mucinous cystadenomas are among the frequently occurring ovarian tumors. RMC shares a histological similarity to ovarian mucinous cystadenomas but can arise at any location in the retroperitoneum without attachment to the ovary. Their biological behavior and histogenesis remain speculative. An accurate preoperative diagnosis of these tumors is difficult because no effective diagnostic measures have been established. Complete surgical resectability usually ensures cure. There exists a theoretical possibility of malignant transformation let alone the high probability of re-acculmulation of cyst fluid in case of aspiration or incomplete surgical resection. Here we report a case of RCM in a post-hysterectomy patient, in which instance the retroperitoneal cyst was aspirated in the first surgical approach, later presenting as a huge cystic mass.

**Keywords:** Primary retroperitoneal mucinous cystadenoma, Post-hysterectomy.

## Introduction:

Any cystic abdominal mass in a woman poses diagnostic challenge in regard to the point of origin of the mass. The probability of retroperitoneal origin should be considered along with common intra-peritoneal masses.[1,2] Subramony et al reported that the estrogen receptor is positive in stromal cells of a RMC implicated in tumour promotion, which could explain the exclusive occurrence of these tumours in women, although three cases of RMC in men have been reported in the literature. The retroperitoneal masses may be of neoplastic or non-neoplastic origin.[3] Pre-operative confirmation of a retroperitoneal mass is seldom possible. Asymptomatic huge cystic mass in a woman may be retroperitoneal; whereas in particular cases certain key clinical points along with CT scan may lead to the correct pre-operative diagnosis. Except for retroperitoneal haematoma/urinoma/TB, almost all require surgical excision for management.[4,5] Here we present a case of post-hysterectomy abdomino-pelvic cyst which was later confirmed a primary retroperitoneal mucinous cystadenoma.

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## Case Presentation:

A 44-year-old multiparous lady presented with swelling of both legs and gradual abdominal distension for 6 months. She had associated mild constant abdominal pain, aggravated by changing posture. The patient also complained of constipation, but her bladder habit was normal. The patient had total abdominal hysterectomy 11 months back, a retroperitoneal cyst was found during that operation, which was aspirated. She was diabetic and hypertensive. Her vital parameters were normal. Abdominal examination revealed gross abdominal distension with an ill-defined cystic mass felt predominantly in the right side of the abdomen. Internal examination revealed a healthy vault with a cystic feeling high up from the vault. Ultrasonogram revealed a large cystic lesion in the right side of the abdomen possibly retroperitoneal in location (suggested by the displacement of bowel and right ureter) with grade-1 fatty change of the liver. CT scan revealed a unilocular sizable thin walled cystic lesion at the right adnexal region, possibly benign ovarian cyst with mild hepatomegaly (Figure 1a and 1b). Investigations revealed CA-125 -6.60 U/ml (reference value of 35 U/ml) and CEA 1.07 ng/ml (reference value of <2.5 ng/ml in non-smoker, <5.0 ng/ml in smoker). CBC, serum electrolytes, serum creatinine, TSH, Serum albumin were normal. After consulting with general surgical colleagues, laparotomy was performed through right lower paramedian incision. A huge retroperitoneal cyst of 20x20 cm was found which contained 2 liters of clear fluid. The entire cyst was removed. Both ovaries were found to be partially cystic and were also removed along with both fallopian tubes. There was minimal adhesion from previous surgery (Figure: 2a, 2b, 2c). Histopathology of the retroperitoneal cyst revealed Mucinous cystadenoma;

on gross appearance the cyst wall was 0.2 cm thick with smooth inner and outer surface. Microscopically the cyst wall was made of collagenous fibrous tissue and was lined by tall columnar epithelial cells with apical mucin. Ovarian histopathology revealed haemorrhagic corpus luteal cyst in one ovary and simple cyst in another ovary. There was no evidence of malignancy in any of the sections examined (Figure:3). Cytopathology of cyst fluid was also negative for malignancy. CEA of the cyst fluid was not done. The patient had an uneventful post-operative convalescence.

**Figure 1:** CT scan of the abdomen showing the cyst extending from the right hepatic flexure into the pelvis

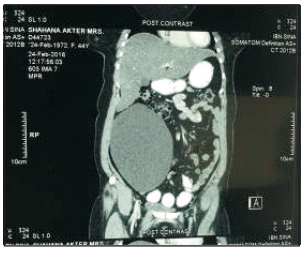

**Fig. 1a:** Sagittal view

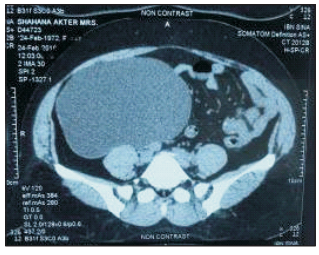

**Fig 1b:** Transverse section at the level of the pelvis

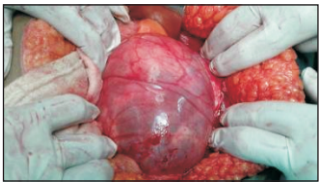

**Fig. 2a:** Per-Operative view showing the cyst itself.

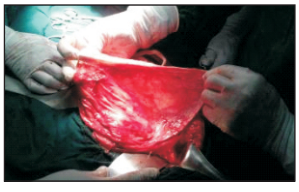

**Fig. 2b:** Per-operative view showing the removed collapsed cyst wall

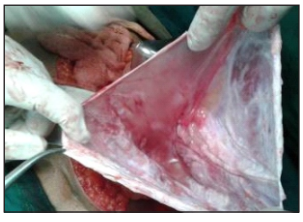

**Fig. 2c:** Per-operative view showing the interior of the cyst.

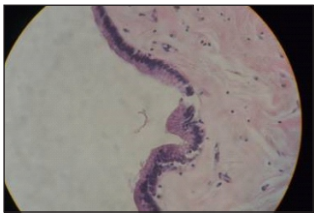

**Fig 3:** Histopathologic view of the lining of the mucinous cystadenoma

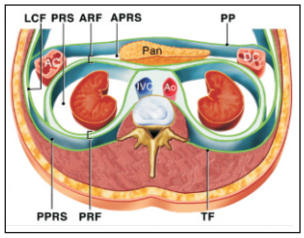


Fig 4: Drawing of the anatomy of the retro-peritoneal spaces at the level of the kidneys. The anterior pararenal space *(APRS)* is located between the parietal peritoneum *(PP)* and the anterior renal fascia *(ARF)* and contains the pancreas *(Pan)*, the ascending colon *(AC)*, and the descending colon *(DC)*. The posterior pararenal space *(PPRS)* is located between the posterior renal fascia *(PRF)* and the transversalis fascia *(TF)*. The perirenal space *(PRS)* is located between the anterior renal fascia and the posterior renal fascia. *Ao* = aorta, *IVC* = inferior vena cava, *LCF* = lateroconal fascia.

## Discussion:

Retroperitoneal cystic mass arises from structures within the retroperitoneal space but outside the major organs of that compartment. The retroperitoneal space is anatomically defined as the space between the posterior parietal peritoneum anteriorly and the transversalis fascia posteriorly. The retroperitoneum extends from the diaphragm superiorly to the pelvis inferiorly. The space is broadly divided into the anterior and posterior pararenal, perirenal, and great vessel spaces. The anterior pararenal space is bordered anteriorly by the posterior parietal peritoneum, posteriorly by the anterior renal fascia (Gerota fascia), and laterally by the lateroconal fascia (Fig-4). The anterior pararenal space contains the pancreas and duodenum (the pancreaticoduodenal space), and the ascending and descending colon (the pericolonic space). The posterior pararenal space is situated between the posterior renal fascia (Zuckerkandl fascia) and the transversalis fascia, whereas the perirenal space is located between the anterior renal fascia and the posterior renal fascia. The great vessel space is the fat-containing region that surrounds the aorta and the inferior vena cava (IVC) and lies anterior to the vertebral bodies and psoas muscles. Below the level of the kidneys, the anterior and posterior pararenal spaces merge to form the infrarenal retroperitoneal space, which communicates inferiorly with the prevesical space and extraperitonealcompartments of the pelvis.[2,4] Because of loose connective tissue in the retroperitoneum, tumors can have widespread extension before clinical presentation, as in our case.

Retroperitoneal lesions according to their histopathologic types have been complied in different reviews highlighting their unique clinical and CT characteristics. Here we present a brief summary of a few.[6-8]

### Neoplastic

Cystic lymphangioma: Multilocular, crosses one or more retroperitoneal compartments. Asymptomatic mass, more common in men.

**Mucinous cystadenoma:** Asymptomatic unilocular mass, occurs in women with normal ovaries. Detailed discussion is carried out in the next section of this article.

**Cystic teratoma:** Presence of fat and calcifications. Asymptomatic, occurs in women.

**Cystic mesothelioma:** Multilocular More common in women associated with abdominal pain.

**Mullerian cyst:** Unilocular or multilocular. Occurs in

obese women who undergohormonal therapy for menstrual irregularity.

**Epidermoid cyst:** Unilocular, occurs in presacral space. Occurs in women; associated with constipation.

**Tailgut cyst:** Multilocular, occurs in presacral space. More common in women, Associated with malignant change.

**Bronchogenic cyst:** Occurs in subdiaphragmatic space. Asymptomatic.

### Cystic change in solid neoplasm

**Paraganglioma:** Usually thick walled, Associated with hypertension.

**Neurogenic tumor**: Usually thick walled, usually occurs in pre-sacral pelvic retro-peritoneum. More common in women.

**Pseudomyxoma retroperitonei:** Multicystic masses with thicked septa and, curvilinear calcifications, occurs in right lower quadrant. Presents with palpable mass and abdominal pain.

**Perianal mucinous carcinoma:** Multicystic masses arround the anus or rectum. Associated with a history of long standing anal fistula.

### Nonneoplastic

**Pancreatic pseudocyst:** Usually occurs in peripancreatic space. Associated with history of pancreatitis, high levels of amylase or lipase.

**Nonpancreatic pseudocyst:** Thick fibrous wall. Asymptomatic.

**Lymphocele:** Occurs after radical lymphadenectomy.

**Urinoma:** Hydronephrosis. Assosciated with history of trauma.

**Hematoma:** May manifest as hyper-attenuating lesion within fluid. Associated with history of trauma.

**Castle man diseases:** Idiopathic retroperitoneal fibrosis.

### Diagnosis and treatment of Retroperitoneal mucinous cystadenoma (RCM)

There are no pathognomonic clinical or radiologic findings for RCM, thus obtaining an accurate preoperative diagnosis with standard imaging modalities is nearly impossible. Based on the review of cases reported in the English literature, most patients presented with asymptomatic relatively large mass and vague abdominal discomfort/ constipation. However, no cases presented with severe abdominal pain.[9,10] Laboratory studies, including serum tumor markers and cytology study of cystic fluid are not helpful in making diagnosis of the tumors. However, Motoyama et al reported that measurement of CEA level in the cystic fluid may be useful in making the diagnosis.[8] With regard to the imaging characteristics of RMCs, these tumors usually manifest as homogenous unilocular cystic masses at CT of the abdomen with mural calcifications, which support the diagnosis of cystadenoma rather than teratoma, as in our case. Furthermore, displacement of colon, kidney or ureter may suggest the retroperitoneal location of tumors.

Primary retroperitoneal mucinous tumors are rare. The most common type of retroperitoneal mucinous tumors is RMC, which shares a histological similarity to ovarian mucinous cystadenomas but can arise at any location in the retroperitoneum without attachment to the ovary. The histogenesis of primary RMCs remains unclear. Four main hypotheses remain with regard to the histogenic origin of retroperitoneal mucinous tumors. The tumor may arise either from ectopic ovarian tissue, from a teratoma in which the mucinous epithelium predominates all other components, or from remnants of the embryonic urogenital apparatus. Recently, the fourth theory has gained wide acceptance.Histologic, immunohistochemical, and electron microscopic examination of the lining epithelial cells showed features of coelomicmesothelial cells, suggesting that these tumors arise from invagination of the peritoneal mesothelial layer that undergoes mucinous metaplasia to form a cystadenoma.[2,11] Furthermore, Subramony et al reported that the estrogen receptor is positive in stromal cells of RMC, which could explain the exclusive occurrence of these tumors in women.[3]

A study on literature review using Medline starting in 1970 upto 2015 found a total of 19 cases of primary RMCs in the English literature and all cases were women, with an age range of 14 to 85 years. The size of reported tumors ranged from 7 cm to 30 cm. There was no relationship between the age of patients and the size of tumors. The symptoms were non-specific and most of the patients complained of asymptomatic mass or abdominal discomfort. Interestingly, the preoperative diagnosis was mesenteric cyst in 4 cases, ovarian cyst in 3 cases, renal cyst in 2 cases and retroperitoneal cystic tumor in one case. Serum levels of tumor markers were normal in 4 cases. However, two cases demonstrated a slight elevation of CA19.9 and CA125 levels, respectively. There was no evidence of recurrence after surgical management in 9 patients.[12,13]

The patient had a pre-operative CEA 1.07 ng/ml (reference value of <2.5 ng/ml in non-smoker, <5.0 ng/ml in smoker). Cyst fliud CEA may be helpful in the pre-operative diagnosis of RCM.[8]

These tumors seem to behave in a benign fashion with no recurrences after complete surgical removal, as demonstrated in our study; the first attempt of aspiration of cyst fluid during hysterectomy resulted in the re-accumulation of cystic fluid and the presentation of 20x20

cm cyst after 4 years of Hysterectomy. The apparent normal looking ovaries at the time of laparotomy; later proven by histopathology to be normal also helped to prove that the cystic mass had no association with the ovaries. Successful laparoscopic excision of a primary RMC has also been reported.[12]

**Surgical approach to retroperitoneal mass:**

As for the management of primary RMCs, complete surgical excision is recommended to eliminate the risk of infection, recurrence, and malignant degeneration. The question regarding resectability of large cystic masses is whether it is beneficial/oncologically sensible to resect the tumour. The crucial balance between patient benefit vs treatment morbidity has been nicely depicted by Dr. Blake Cady: "In the field of surgical oncology: tumour biology is king, patient selection is queen, and technical manoeuvres are the prince and princess. Occasionally the prince and princess try to overthrow the powerful forces of the King and Queen, sometimes with temporary apparent victories, usually to no long term avail."[14-16] Therefore masses with the Clinical and or CT /sonograhic parameters of benign nature should be operated with the intent of complete removal/enucleation to avoid re-accumulation of cyst fluid and the small but potential risk of malignancy withina focus of the benign mass.

## Conclusion:

Gynaecologists frequently encounter post-hysterectomy patients presenting with cystic lesions in the pelvis. Residual ovarian cyst, endometriotic cysts, let alone benign/malignant ovarian masses are the common differentials to be excluded at first line. The entire range of retroperitoneal cystic lesions should also be kept in mind particularly RCM which occurrs exclusively in female. The sensitivity of pre-operative prediction of the histologic type of the lesion can sensibly guide the surgeon regarding the operative radicality/patient morbidity. The higher suspicion of malignancy pre-operatively as reflected by the CT findings, CEA values can opt for chemoradiation rather than surgical venture in such an anatomically diverse space posing potential risks of major vessel/ureteric damage. The small number of globally registered cases and insufficient surveillance data regarding diagnosis and management show that there is a need for effective registration and further study of these rare diseases.

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# Case Report

## Polyglandular Syndrome Type II: A Case Report

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## Abstract

Associations of multiple autoimmune endocrine disorders have been classified in different syndromes. An autoimmune polyglandular syndrome (APS) is divided into 2 major subtypes based on age of presentation, pattern of disease combinations and mode of inheritance. APS type I and type II (APS-I and -II) can be clearly separated clinically. APS-II (Schmidt's syndrome) is defined by the coexistence of autoimmune Addison's disease with autoimmune thyroid disease and/or type 1 diabetes mellitus. A fraction of the patients also present with or later develop other organ specific autoimmune disorders. These include hypergonodotropic hypogonadism, vitiligo, pernicious anaemia, myasthenia gravis and celiac disease. APS-II usually manifest in 3rd or 4th decade of life with female preponderance. We report here a case of APS-II in a 35-year-old female who initially presented with diabetes mellitus (DM), which was soon followed by hypothyroidism, premature ovarian failure and vitiligo.

**Keywords:** Polyendocrinopathies, Diabetes mellitus, Autoimmune thyroid disease.

## Introduction:

APS include involvement of multiple endocrine glands. In patients with these syndromes, hypofunction of multiple endocrine glands is induced by autoimmunity and occurs in well-described patterns. APS-I is an autosomal recessive disorder, the first symptoms usually appear during childhood, but the full picture is shaping up to the age of 20.[1,2] Also known as APECED, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, APS-I is characterized by the triad of chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism, and adrenal insufficiency.[3] APS-II is the most common form of autoimmune polyendocrinopathy. The modality of transmission is complex and polygenic.[1] APS-II affects women in a 3:1 ratio to men.[3] APS-II is diagnosed when at least two of the following are present: adrenal insufficiency, autoimmune thyroid disease (thyroiditis with hypothyroidism or Graves disease with hyperthyroidism), and type 1 diabetes.[3] Other autoimmune diseases characteristic for the APS-II are: primary hypogonadism, myasthenia gravis, celiac disease, pernicious anemia, alopecia and vitiligo[1,2].

## Case Presentation:

A 35-year-old lady presented to the endocrinology department with the complaints of generalized weakness, polyuria and polydipsia. She had also history of amenorrhea and hot flush for last 10 years. But, had no symptoms of nausea, vomiting, chronic diarrhea, loss of consciousness. On examination, she was mildly anemic, BMI-16.4 $Kg/m^2$, vital signs were normal, diffusely enlarged thyroid, inner surface of both lips were hypopigmented (mucosal vitiligo). Systemic examination was unremarkable. On biochemical evaluation she was found to have diabetes on the basis of high plasma glucose. Patient was treated with intravenous fluid and insulin. Further investigations showed hypothyroidism as evident by low $FT_4$ and high thyroid stimulating hormone (TSH). High titer of auto antibodies was present along with this hypothyroid profile. Consequently, a replacement therapy with levothyroxine 50μg/day was initiated and the dose was gradually increased. Basal cortisol level was measured to rule out adrenocortical insufficiency prior treatment with levothyroxine. High level of follicle stimulating hormone (FSH) and leutinizing hormone (LH) were indicating premature ovarian failure. Her pelvic ultrasonography revealed no pathology in the uterus and in ovaries. She began to receive hormone replacement therapy. She had been advised for regular follow up. Laboratory parameters are shown in Table-1.

The patient was considered to have APS-II because of presence of Hashimoto's thyroiditis, Diabetes mellitus (probably LADA) and premature ovarian insufficiency (Primary hypogonadism), vitiligo (Fig-1).

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**Table 1:** Laboratory finding of the patient.

| Tests | Results | Reference Range |
|---|---|---|
| Haemoglobin | 13.6 g/dl | |
| Fasting Plasma Glucose | **23.1** mmol/l | |
| 2 hour after 75 gm glucose | **32.7** mmol/l | |
| Urine for ketone Body | Negative | |
| HbA1c | **13.7 %** | |
| Total Cholesterol | **298** mg/dl | |
| HDL | 45.1 mg/dl | |
| LDL | 92.9 mg/dl | |
| TG | **800** mg/dl | |
| FT4 | **0.70** ng/dl | 0.8-1.8 ng/dl |
| TSH | **40.5** µIU/ml | 0. 35-5.5 µIU/ml |
| Anti Thyroglobulin Ab | <20.0 IU/ml | Up to 40 IU/ml |
| Anti Thyroid peroxidase Ab | **681** IU/ml | Up to 35 IU/ml |
| FSH | **118** mIU/L | Post menopause-21.7-153 mIU/L |
| LH | **49.5** mIU/l | Post menopause-11.3-39.8 mIU/L |
| Cortisol | 475 nmol/l | 138-690 nmol/l |

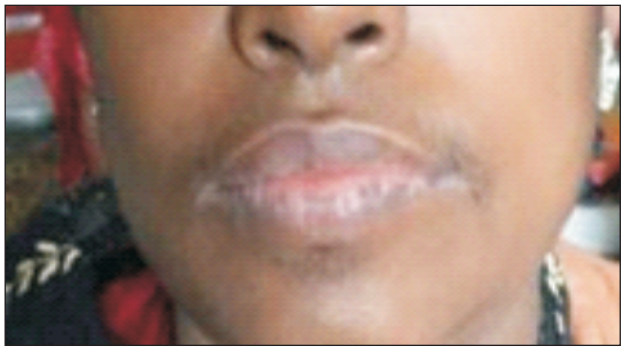

**Fig 1:** Mucosal Vitiligo

## Discussion:

Polyglandular autoimmune syndrome type II is hereditary in around half of cases, and various forms of genetic transmission are described (recessive autosomic, dominant autosomic and polygenic). Historically, Schmidt (1926) first described the association of Addison disease and thyroiditis. Later, Type 1 diabetes was included in the syndrome by Carpenter and coworkers in 1964.[3] Other components of APS-II include the following: primary hypogonadism, myasthenia gravis, celiac disease, pernicious anemia, alopecia, vitiligo, and serositis. The most frequent association appears to be with type 1 (over 50%) and autoimmune thyroid disease (70% in some series).[3] Our patient had four components i.e. DM, autoimmune thyroiditis, primary hypogonadism, vitiligo. But, no feature of adrenal insufficiency was found at the time of diagnosis. Adrenal insufficiency may be concurrent, may be delayed in onset for up to two decades, or may never manifest.[8] APS is considered to be multifactorial with both environmental and host factor playing interplay to trigger autoimmunity against endocrine glands. Organ-specific antibodies may present even in the absence of overt disease.[4] These antibodies points towards ongoing destruction of endocrine tissues that eventually leads to secretary insufficiency and overt clinical disease. Therefore, the clinical presentations of various APS components are preceded by a latent period of months to years.[4] In the majority of patients (around 50%), diabetes mellitus type 1 (DM1) is the first manifestation of polyendocrinopathy,[5] appearing after autoimmune thyroiditis, sometimes simultaneously with Addison disease.[6] In this patient, DM is late onset, dependent on insulin, no features of insulin resistance and associated with other autoimmune endocrine disease, oriented the diagnosis towards LADA (Latent Autoimmune Diabetes in Adults). LADA is a form of autoimmune DM to be considered within the spectrum of diabetes in adults. The term is disputed by some authors, as diagnostic criteria are not very clear, and confirmation of diagnosis requires quite expensive investigations. In LADA, it is recommended to use oral drugs before proceeding to insulin therapy but it is highly important to initiate therapy with insulin at the right time.[5,6] Ovarian failure may be present in 10% of women with APS type II and should be considered in the differential diagnosis in case of amenorrhea in women below 40 years of age.[7] Routine screening for organ specific antibodies is debatable. Dittmar and Kahaly have proposed a diagnostic approach in their study towards screening of patients with APS. First the functional screening of baseline hormone levels including TSH, FSH, LH, free T4, testosterone, estradiol, basal cortisol, glucose, and complete blood counts and electrolytes should be done. Further, detecting organ-specific autoantibodies by screening identifies the patients who may develop autoimmune polyendocrinopathies. These include autoantibodies to islet cells, glutamic acid decarboxylase, IA2, thyroid peroxidase, thyroglobulin, TSH receptor, cytochrome P450 enzymes, parietal cells, intrinsic factor, endomysium, transglutaminase and gliadin. According to the literature, genetic screening is also more useful for APS-I than APS-II. Patients with monoglandular autoimmune endocrinopathy, functional screening for APS should be done every 3 years until the age of 75.[4]

## Conclusions:

Patients with an autoimmune disease should be considered at risk for the other autoimmune diseases. APS-I than APS-II should be monitored for the rest of their lives. Monitoring involves physical examination and some tests, as well as educates the patients (and their relatives) regarding the symptoms and early signs of the major components of the syndrome. It is not always easy to diagnose the type of DM, particularly if the disease is

diagnosed in patients aged between 30 and 40 years. Physician should be cautious in managing patients with APS II as initiating thyroxine supplements without investigating for possible coexistence of underlying adrenal insufficiency may prove to be fatal. Early detection of the disease may reduce morbidity and mortality significantly in the patients with autoimmune polyglandular syndrome.

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# College News

## College Events:

- The commencement ceremony of 1st year MBBS students (BM-32) in MBBS course, session: 2017-2018, was held on 10th January 2018 in the campus of Bangladesh Medical College.
- The National Mourning Day was observed in Bangladesh Medical College and Hospital on 15th August, 2017, 42nd death anniversary of Father of Nation Bangabandhu Sheikh Mujibur Rahman. Teachers, doctors, students and staffs participated in that event. Another discussion meeting and prayer was held on 19th August, 2017 in the college campus for paying tributes to Father of Nation.
- A joyous rally was held on 25th November, 2017 on account of achieving the recognition of the historic 7th March, 1971, speech of Father of Nation Bangabandhu Sheikh Mujibur Rahman as a part of world's documentary heritage by UNESCO.
- The great "Victory Day" was celebrated on 16th December, 2016 in the Bangladesh Medical College and Hospital premises.

## Seminar in BMC:

- A seminar on **"Diabetes mellitus and basis of management"** was held on 14th November, 2017. The speaker was Dr. Yasmin Aktar, MD (EM), Consultant Endocrinologist of BMCH.

## Participation in the International Conferences/Seminars/Workshop/ Congress/Meetings:

- Prof. Dr. Md. Fazlul Kadir, Professor, Dept. of Medicine, Bangladesh Medical College attended the 69th Annual Conference of Cardiological Society of India held from 30th November to 3rd December, 2017 at Kolkata, India.
- Prof. Dr. Zafor Md. Masud, Professor and Head of the Dept. of Oncology, Bangladesh Medical College attended the San Antenio Breast Cancer Symposium held from 5th to 10th December, 2017 in USA.
- Prof. Dr. Sharmeen Yasmeen, Professor and Head of the Dept. of Community Medicine, Bangladesh Medical College attended and presented scientific paper in the 1st World NCD Congress, held from 4th to 6th November, 2017 at Chandigarh, India.
- Prof. Md. Ashraful Islam, Professor and Head of the Dept. of ENT, Bangladesh Medical College attended the 2nd Congress of Asia-Pacific Society of Thyroid Surgery (APTS2017) held on 1st to 3rd November 2017 in Japan.
- Prof. Dr. Raihana Begum, Professor (Current Charge), Dept. of Community Medicine, Bangladesh Medical College attended and presented scientific paper in the Asian Conference on Diarrheal Disease & Nutrition (ASCODD) on 30th October to 1st November 2017 held at India.
- Dr. Md. Tarek Alam, Associate Professor, Dept. of Medicine, Bangladesh Medical College attended the Asian Pacific Society of Respirology Congress held on 23rd to 26th November 2017, at Sydney, Australia.
- Prof. Dr. Md. Zahid Hasan Bhuiyan, Professor, Dept. of Urology, Bangladesh Medical College attended the "37th Congress of the Society International of Urology held from 19th October to 22nd October, 2017 at Portugal.
- Prof. Dr. M. Touhidul Haque, Professor and Head of the Dept. of Cardiology, Bangladesh Medical College attended the World Congress of Eco Cardiology held from 4th to 8th October, 2017 in Jaipur, India.
- Dr. Kamruzzaman, Associate Professor and Head of the Dept. of Orthopaedics, Bangladesh Medical College attended the Orthopaedics Conference held at USA.
- Prof. Dr. M. Touhidul Haque, Professor and Head of the Dept. of Cardiology, Bangladesh Medical College attended the European Society of Cardiology (ESC) Congress 2017, held from 26th to 30th August, 2017 in Barcelona, Spain.

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