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Article published electronically ahead of the print version: Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002 Nov 15; 100(10):3828-31. Epub 2002 Jul 5.

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Original Article

Factors Affecting Successful Creation of Arterio-venous Fistula for Hemodialysis

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Abstract

The preferred vascular access method for efficient hemodialysis is the arterio-venous fistula (AVF). There is a rising trend in AVF establishment conducted by nephrologists, aiming to alleviate the workload of vascular surgeons and expedite the prompt care of individuals afflicted with end-stage renal disease (ESRD). This descriptive observational study was conducted at the Department of Vascular Surgery, Ibrahim Cardiac Hospital and Research Institute during the period of June 2017 to July 2022. During the data collection period 1700 patients sought care in the Department for arterio-venous fistula creation, among them complete data of 1103 patients were included in this study. Majority of chronic kidney disease (CKD) patients were referred from the Department of Nephrology, BIRDEM for AVF creation in the mentioned timeline. Data were collected pre-designed data collection sheet and data were analyzed using Statistical Package for Social Sciences (SPSS) version- 25. This study shows that most of the patients (80.8%) were in ages 30 - 59 years and more than two-third (67.6%) of them were male; male-female ratio was 2:1. Diabetes mellitus (DM) was detected in nearly half of the patients (47.2%) and more than two-third (67.2%) of them were suffering from hypertension (HTN). Higher failure rate (73.3%) of AVF creation among patients of age group 30-59 years, which was significant. Failure rate for male patients was 57% and female patients was 43%. The AVF creation failure rates were 100% for patients with hypertension and for diabetes patients was 60.5%. Complications were found in 15.2% of patients. Post-operative edema and hematoma formation were more common (3.2% and 3.5%, respectively) in comparison to other complications. Among the complicated cases, 7 patients (4.2%) required intervention to correct stealing syndrome and AVF salvage was attempted in 43 cases (25.6%); medical management was pursued in 32(19.0%) cases. Majority (51.2%) of cases who were experiencing complications required AVF ligation. This research demonstrates that several significant clinical factors influence the successful establishment of an arterio-venous fistula (AVF) for hemodialysis factors include advanced age, being male, having diabetes (DM) and hypertension (HTN), having a history of Maintenance Hemodialysis (MHD) prior to AVF creation, choosing the wrist or arm as the AVF site, utilizing specific veins (cephalic and basilic) and specific arteries (radial and brachial).

Keywords: *Arterio venous fistula (AVF), end stage renal disease (ESRD), creatinine clearance rate (CCR), maintenance hemodialysis (MHD)*

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INTRODUCTION

The incidence of chronic kidney diseases is increasing at a galloping rate, particularly with the expanding number of hypertension and diabetes mellitus. Along with higher rates of chronic kidney diseases, End Stage Renal Diseases (ESRD) are also escalating, which requires maintenance hemodialysis. To avail hemodialysis among ESRD patients, successful creation of Arterio-venous fistula (AVF) is essential. In last few years, a good number of AVF creation surgery was performed at Department of Vascular Surgery, Ibrahim Cardiac Hospital & Research Institute. Successful AVF creation depends upon a number of factors. Present study will outline the effects of numerous variables on the results of AVF creation in Bangladeshi population as well as the important parameters to take into account. The aim of this study is to review the experience of creating AVF and to assess its success rate and common complications.

Chronic kidney disease (CKD) is the 16th leading cause of demise worldwide identified as a major public health problem globally and the prevalence is projected to increase continually. In Asia, approximately 434.3 million people had End-Stage Renal Disease (ESRD) that is about 60% of the global population; who are seeking medical attention.[1] According to the National Journal Database, until December 2019, the overall prevalence of CKD in Bangladeshi people was of 22.48%, which was higher than the global prevalence of CKD.[2] Chronic kidney disease includes five stages of kidney damage, from mild kidney dysfunction to complete failure. Generally, a person with CKD stage 5 is considered as End stage renal disease, who eventually needs hemodialysis.[3] To serve this huge population, creation of AVF for hemodialysis is mandatory as the opportunities for kidney replacement surgery is limited in our country.[4] Being a specialized center, at Vascular Surgery Department, Ibrahim Cardiac Hospital & Research Institute thousands of AVF have been created for advanced stage CKD patients in last five years.

A reliable and smoothly operating vascular access for hemodialysis (HD) especially the Arterio-venous fistula (AVF) is the lifeline for an ESRD patient. Failure to create a well-functioning AVF is an obstacle for hemodialysis that will be declining the life expectancy of the huge population suffering from ESRD. From this study multiple variables can be analyzed related to a successful AVF creation and unfavorable factors adversely affecting the outcome can be overcome.[5]

Previously different researches has been done in the different corner of the world. In the Asian context, several studies on outcomes of AVF creation among hemodialysis patients has been under taken at India, Japan, Iran etc. but the study population were not big enough to reflect the huge population.[5-8] Again the studies that were done earlier in Bangladeshi context were of limited sample size. So the outcomes that arrived from those studies cannot be generalized. The study has been conducted to analyze data from larger population of Bangladesh, that will be reflecting the common demographic characteristics, beneficial and the contrary variables of AVF creation for hemodialysis among the Bangladeshi population. On the other hand this research will enrich the epidemiological background of ESRD patients seeking for AVF creation, in our subcontinent. So the present study was under taken to determine the factors responsible for successful outcome of AVF creation.

MATERIALS AND METHODS

This research was designed as a descriptive observational study derived from the Department of Vascular Surgery, Ibrahim Cardiac Hospital and Research Institute. The Data used in this study was obtained from the time period June, 2017 to July, 2022. During that period about 1700 patients visited Dept. of Vascular surgery for arterio-venous fistula creation, among them complete data of 1103 patients were included in our study. Majority of chronic kidney disease (CKD) patients were referred to us from the Department of Nephrology, BIRDEM for AVF creation in the mentioned timeline (June, 2017 to July, 2022). These patients were of both sexes (male or female), of any age. Bangladeshi individual may or may not be undergoing maintenance hemodialysis. Follow-up details were obtained during the Out Patient Department (OPD) visits. The data extracted from hospital records included the patient's demographic details, comorbidities, site and type of AVF, operative details, patency and fistula-related complications.

Data analysis was done projecting multiple variables, that are age group, gender, type of AVF created, site of AVF, artery and vein used, hemodialysis prior to AVF creation, the co-morbidities like DM, HTN and the relative complications along with their corrective surgery.

Statistical analysis

Data were collected by pre-designed data collection sheet. Complete history and documentations were reliable enough to perform the Data Collection. Then the Data was analyzed by using SPSS for windows version 25. Descriptive statistics were expressed in frequency, percentage, arithmetic mean. For inferential statistics, chi-square test was performed to explore the association between categorical variables. Multivariable logistic regression analysis was carried out in order to determine the relationship between various components. The confidence interval was set at 95% and the significance level was set at less than 0.05 (p0.05).

RESULTS

Table I contains the baseline characteristics of the patients, these are- 80.8% were age of 30 to 59 years and 67.6%

were male. Diabetes Mellitus (DM) was observed in 47.2%, hypertension in 67.2%. Here 82.7% had undergone maintenance hemodialysis (MHD) before arterio-venous fistula creation. Jugular access was observed in 34.7% of cases and femoral access in 48% cases. Notably, radio-cephalic fistulas at the wrist accounted for 47.9% of cases, and brachio-cephalic fistulas constituted 35.1%.

Table- I: Baseline Characteristics of the Patients (n=1103)

Characteristics		Frequency	Percentage
Age in years			
	<30	74	6.7
	30-59	891	80.8
	>60	138	12.5
Mean ±SD		47.49±11.61	
Sex			
	Male	746	67.6
	Female	357	32.4
DM		521	47.2
HTN		741	67.2
MHD (before AVF creation)		912	82.7
Type of vascular access before AVF			
	Jugular	383	34.7
	Femoral	529	48.0
Types of AVF			
	Anatomical snuff box fistula	11	1.0
	Radio-cephalic fistula at wrist	528	47.9
	Radio-cephalic fistula at mid-forearm	23	2.1
	Brachio-cephalic fistula	387	35.1
	Brachio-basilic transposition fistula	141	12.8
	Brachio-axillary translocation fistula	02	0.2
	PTFE graft fistula	07	0.6
	Ulnar-Basilic fistula	01	0.1
	Ulnar-Ulnar U loop fistula (PTFE Graft)	02	0.2
	PTA to GSV fistula	01	0.1

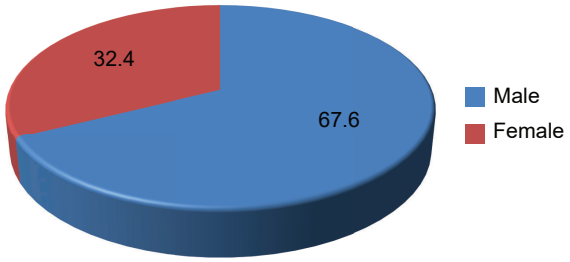


Figure- 1: Sex distribution of the patents

Figure 1 shows 67.6% were male and 32.4% were female.

Table II represents the anatomical details of the study subjects who underwent AVF creation; 48.8% and 49.0% of AVFs were created at the wrist and arm respectively. Veins were used the cephalic vein (74.5%), radial artery (51%) and brachial artery (48.7%).

Table- II: Anatomical details of the study subjects who underwent AVF creation (n=1103).

		Frequency	Percentage
Site of AVF	Wrist	539	48.8
	Forearm	23	2.1
	Arm	540	49.0
	Lower limb	01	0.1
Vein	Cephalic vein	822	74.5
	Ante Cubital vein	127	11.5
	Basilic vein	144	13.1
	Great saphenous vein	01	0.1
	PTFE Graft	09	0.8
Artery	Radial artery	562	51.0
	Brachial artery	537	48.7
	Ulnar Artery	03	0.3
	Posterior tibial artery	01	0.1

Table III describes the factors associated with AVF creation using Chi-square test; the failure rate of patients was 73.3% in age group 30-59 years and it was significant. Failure rate among males were 57%. Failure rate of diabetic patients was 60.5% and HTN 100%. Patients on maintenance hemodialysis were 100% failure rate and arm site of AVF was failure rate 53.5%. Cephalic vein was failure rate 57% and radial artery was 74.4%.

Table- III: Factors associated with AVF creation using Chi-square test (n=384)

Factors or the Patient's Characteristics		Outcome		P value
		Success (n=1017)	Failure (n=86)	
Age	<30 (74)	74(7.3%)	0(00)	0.001
	30-59 (863)	828(81.4%)	63(73.3%)	
	>60 (166)	115(11.3%)	23(26.7%)	
Sex	Male	697(68.5%)	49(57%)	0.028
	Female	320(31.5%)	37(43%)	
DM	Yes	469(61.1%)	52(60.5%)	0.010
	No	548(53.9%)	34(39.5%)	
HTN	Yes	655(64.4%)	86(100)	0.001
	No	362(35.6%)	0(00)	
MHD (before AVF creation)	Yes	826(81.2%)	86(100)	0.001
	No	191(18.8%)	0(00)	
Site of AVF	Wrist	501(49.3%)	38(44.2%)	0.821
	Forearm	21(2.1%)	2(2.3%)	
	Arm	494(48.6%)	46(53.5%)	
	Lower limb	1(0.1%)	0(00)	
Vein	Cephalic vein	773(76%)	49(57%)	0.001
	Ante Cubital vein	112(11%)	15(17.4%)	
	Basilic vein	122(12%)	22(25.6%)	
	Great saphenous vein	10(1%)	0(00)	
Artery	Radial artery	498(49%)	64(74.4%)	0.001
	Brachial artery	515(50.6%)	22(25.6%)	
	Ulnar Artery	3(0.3%)	0(00)	
	Post. tibial artery	1(0.1%)	0(00)	

Table IV states the predictive factors of successful outcomes after arterio-venous fistula creation; here age, gender, DM, HTN, artery and vein was a significant predictor of AVF success (P=0.001, 0.029, 0.011, 0.001 and 0.004)

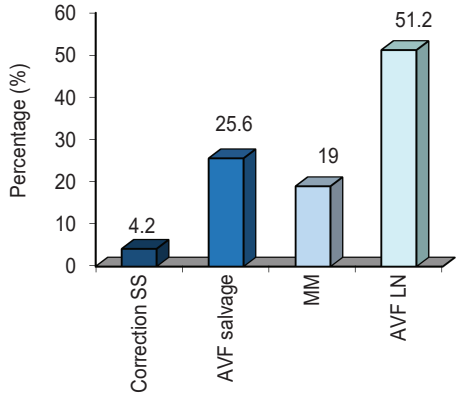
Table- IV: Predictive factors of successful outcomes after arterio-venous fistula creation

Variables	Coefficient	Standard error	P-value	Odds Ratio
Age	1.052	0.263	0.001	2.863
Gender	0.498	0.228	0.029	1.645
DM	0.581	0.229	0.011	1.560
HTN	0.594	0.241	0.016	1.551
Site of AVF	0.166	0.210	0.428	0.847
Artery	0.902	0.221	0.001	2.464
Vein	0.378	0.133	0.004	1.459

Table V shows the summary of the complications in the study. A total of 15.2% patients had complications; among them post-operative edema and hematoma formation were (3.2% and 3.5%, respectively.

Table-V: Summary of the complications in the study (n=1103)

Complications	Frequency	Percentage
Post-operative Bleeding	24	2.1
Post-operative Edema	35	3.2
Hematoma Formation	39	3.5
Pseudoaneurysm Formation	23	2.1
Thrombosis	29	2.6
Post-operative cellulitic changes	11	1.1
Stealing Syndrome	07	0.6
No complication	935	84.8



NB: SS=Stealing Syndrome, MM=Medical management, LN= Ligation needed

Figure- 2: Summary of outcome of the complicated Cases in this study (n=168)

Figure 2 depicts the summary of outcome of the complicated cases in this study. Among the complicated cases, 7 patients (4.2%) required intervention to correct stealing syndrome and 43 cases (25.6%) AVF salvage was attempted, medical management was pursued in 32 cases (19.0%) and majority of cases experiencing complications (51.2%), AVF ligation was required.

DISCUSSION

The procedure of arteriovenous fistula holds significant importance for vascular surgeons. As the global demand for hemodialysis increases among patients with end-stage renal disease (ESRD), arteriovenous fistulas (AVF) have gained prominence as the preferred vascular access method due to their extended functionality, increased resilience, and lowered infection risk.[9]

This study shows the majority of patients constituting 80.8% were the ages of 30 to 59 years. A notable proportion, 12.5%, were aged 60 or older, while 6.7% were under the age of 30. This findings consistent with several previous studies.[3-7]

As reported in the study by Sichona et al.[10] the research identified patients within the higher age bracket of 50 to 59 years. These results are further supported by earlier investigations conducted in Europe, which also indicated that advanced age was associated with older patients, typically those aged over 65 years.[11]

The gender distribution observed in this study, where males constituted 67.6% and females 32.4%, mirrors the gender imbalance frequently documented in kidney disease populations across various studies.[4-9] This gender disparity has sparked investigations into whether hormonal differences, genetic factors, or disparities in healthcare-seeking behavior contribute to the observed pattern. Also found that the outcome among males was more successful (p=0.001). This findings are well agreement with other studies.[6-12]

This study shows patients with hypertension and diabetes were more likely to have AVF failure rate. The findings of this study consisted with previous studies.[7-12] Other studies, on the other hand, found that hypertension was not a significant risk factor for AVF creation. Another study reported diabetes represents an ever-growing cause of ESRD.[5] In the past, even though diabetes was considered a risk factor for Arterio-venous fistula non-maturation, several studies have reported successful outcomes in diabetic patients.[12-14] Sedlacek et al. concluded that diabetes didn't independently contribute to AVF non-maturation, and its presence didn't impact the success of AVF creation.[15] Allon et al. similarly found that both diabetes and age didn't affect AVF maturation outcomes, although they were both significantly linked to increased intimal hyperplasia.[13] In a similar vein, Farber et al. discovered that diabetes wasn't connected to early thrombosis.[16] Conversely, Salmela et al. noted that diabetes mellitus, female gender, and thrombophilia were associated with decreased primary fistula patency rates.[12]

This study shows MHD (before AVF creation), wrist site of AVF, arm site of AVF, cephalic vein, basilic vein, radial artery and brachial artery were more likely to have AVF

failure rate. This study's findings are consistent with prior research, which found that MHD (before AVF creation), wrist site of AVF, arm site of AVF, cephalic vein, basilic vein, radial artery and brachial artery had a greater main failure rate arterio-venous fistula for hemodialysis.[8-12] Previous studies examined MHD, wrist site of AVF, arm site of AVF, cephalic vein, basilic vein, radial artery and brachial artery main factor of affecting successful creation of Arterio-venous fistula for Hemodialysis.[14,15] Prospective observational study results have shown that wrist site of AVF, arm site of AVF, cephalic vein, basilic vein, radial artery and brachial artery linked to a higher factor of Arterio-venous fistula for Hemodialysis.[17] A prospective study by V. Wong et al assessed the radial arteries and cephalic veins found that fistula failure was associated with cephalic vein and radial artery.[18]

This study shows Hematoma formation was the common complication present i.e. in 39 (3.35%) then post-operative edema (3.2%), thrombosis (2.6%), pseudoaneurysm formation (2.1%) and post-operative bleeding 2.1%). Similar studies Moloti reported out of the total 15 unsuccessful AV fistula, thrombosis was the major complication present in 10 (22.22%) AVF, least complication was wound infection and vessel blowout, out of which the vessel blowout was a result of trauma and the patient had sustained.[19] In a study by Qing Y et al. conducted in Shanghai First People's Hospital affiliated to Jiaotong University reported that the most frequent complication seen following creation of an AV fistula was thrombosis (13.86%).[29] Previous studies examined complications related to AVF construction and reported venous thrombosis rates as high as 58%, with a susceptibility for thrombosis in the cephalic and basilic veins.[20, 21]

This study shows that AVF ligation needed emerges as the most prevalent complication among the cases, occurring in 51.2% of the total cases. On the other hand, the complication with the lowest frequency and percentage is the correction of stealing syndrome which appeared in only 4.2% of the cases. The category of AVF salvage is notable as well, appearing in 25.6% of the cases. The medical management category, accounting for 19.0% of cases, raises questions about the nature of complications that necessitated non-surgical interventions. Similar study Moloti et al.[19] reported out of the 10 AVF complicated by thrombosis, 6 AVF were treated with surgical thrombectomy.

LIMITATION

- Inadequate data regarding arterial & venous diameter.
- Certain parameters like clinical laboratory parameters were not included and hence their role or bias could not be determined.

CONCLUSION

This research presents findings that highlight the significance of certain clinical factors in the successful establishment of arteriovenous fistulas (AVFs) for hemodialysis. These factors encompass older age, male gender, diabetes (DM), hypertension (HTN), pre-existing heart disease (MHD) prior to AVF creation, AVF placement at the wrist or arm sites, utilization of specific veins (cephalic and basilic), as well as particular arteries (radial and brachial). Additionally, the study underscores the necessity for meticulous planning by a vascular surgeon and the thoughtful selection of patients in collaboration with nephrologists when considering AVF creation. This approach is advocated to enhance the positive outcomes of AV access, thus promoting greater utilization of AV fistulas as the primary mode of access for hemodialysis in end-stage renal disease cases. To facilitate this, the study supports the establishment of a specialized renal access clinic. This clinic would serve as a dedicated platform for comprehensive AVF creation planning, incorporating pre-operative Doppler scans and offering the evaluation of challenging access scenarios before the surgical procedure.

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Original Article

Clinical Presentation of Patients with Hepatocellular Carcinoma in a Tertiary Level Hospital of Bangladesh

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75% - 86% of all cases. Men are affected approximately two to three times more than women. It is considered as the fifth most common cancer in men and the ninth in women. The prognosis for liver cancer is very poor which has made it globally the second most common cause of death from cancer. The highest liver cancer rates are found in East and Southeast Asia and in Middle and Western Africa. Western world is complaining of rising HCC prevalence as a result of migration from HBV-endemic regions, hepatitis C virus (HCV) infection, alcoholic cirrhosis, and non-alcoholic steatohepatitis associated with the obesity epidemics. The accurate diagnosis of HCC dependent on clinical presentation, biochemical, imaging, cytological and/ or histopathological examination. This was a descriptive study of hepatocellular carcinoma patients those attended Dhaka Medical College Hospital and Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh from September 2006 to march 2008. Thirty (30) consecutive biopsy proven hepatocellular carcinoma patients were enrolled in this study. This study collected data by reviewing Medical records (prescriptions and diagnostic reports) and interviewing patients for various present symptoms/ signs, past complaints (symptoms/ signs) they experienced in different duration and for confirmation of HCC. Among the symptoms almost all 29(96.66%) of the patients had experienced loss of appetite and most of the patients were experienced generalized weakness 28(93.33%) followed by weight loss 24(80%). More than two-third of the patients had complained abdominal pain 22(73.33%), abdominal fullness 21(70%), abdominal mass 20(66.66%) and nausea and vomiting 20(66.66%). Various signs of HCC were found in examination during interview and from their past experience/ reviewing medical record of illness; where most of them 27(90%) had hepatomegaly and half of them 15(50%) had splenomegaly and ascites. Among the others sign of HCC, one-third (33.33%) of them had yellow discolouration of eyes, yellowish urine, jaundice and fever. Several signs were also observed like Leg swelling 9(30%), cough 8(26.66%), alteration of bowel habit 6(20%). Signs like blood vomiting 1(3.33%) and leg oedema 4(13.33%) were also observed. Information regarding clinical presentation from this study may be utilized as indicator for referral, case definition in research works and probable diagnosis of HCC. This clinical presentation may be a strong tool for symptomatic surveillance of HCC and prevention of HCC including chronic hepatitis B and chronic hepatitis C virus infection.

Keywords: *Hepatocellular carcinoma, clinical presentation, loss of appetite, generalized weakness, weight loss.*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary liver malignancy and one of the most common cancers worldwide and is one of the leading causes of cancer-related death.[1–3] HCC is the most common type of primary liver cancer, accounting for 75% - 86% of cases[4]. Men are affected approximately two to three times more than women, with higher incidence and mortality across most countries.[5] It is considered as the fifth most common cancer in men and the ninth in women. The prognosis for liver cancer is very poor which has made it globally the second most common cause of death from cancer.[6]

The highest liver cancer rates are found in East and Southeast Asia and in Middle and Western Africa.[7] This difference in incidence of liver cancer between different geographical regions and countries is mainly attributed to difference in the incidence of underlying risk factors: viral hepatitis, alcohol use, occupational exposure; and

nonalcoholic fatty liver disease (NAFLD).[8–13] HCC is secondary to liver cirrhosis in 80% of patients and is the main cause of death in liver cirrhosis patients in Europe.[14] Additionally, the Western world is complaining of rising HCC prevalence as a result of migration from HBV-endemic regions, hepatitis C virus (HCV) infection, alcoholic cirrhosis, and non-alcoholic steatohepatitis associated with the obesity epidemics.[15] Only 30–40% of patients present with early-stage disease amenable to curative treatments, such as resection or liver transplantation (LT), while others can only undergo local therapies or palliative care.[14] .

Bangladesh is a developing country in Asia with a population of 170 million. It is estimated that more than 8 million people are chronically infected with HBV[16] and about 1 to 2 million with HCV.[17] Khan M et al have detected 18.75% liver cirrhosis patients developed HCC by examining a cohort of 64 patients at Bangladesh in 1997[18]. Another study conducted in United Kingdom, among HCC patients of Bangladeshi origin, has shown that 36 % and 56% of these patients have been infected with HBV and HCV, respectively.[19] However, studies from India, a close neighbour of Bangladesh, have reported that about 80% HCC patients are infected with HBV and most of the HCC patients are cirrhotic.[20] These studies indicate that more investigations are required to develop insights about clinical features, etiological agents and epidemiology of HCC at Bangladesh.

MATERIALS AND METHODS

This is a descriptive study with present and prospective documentation of cases. Randomly selected 50 cases of suspected hepatocellular carcinoma those attended the Dhaka Medical College Hospital and Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh, from November 2007 to September 2008 were taken for this study. Finally 30 consecutive biopsy proven hepatocellular carcinoma patients were enrolled in this study.

A questionnaire was prepared with baseline characteristics of the patients with HCC and presenting signs/ symptoms of the patients. This was filled up by asking questions, examination and reviewing record (prescription/ diagnostic report) of the patients. The diagnosis of underlying liver cirrhosis was done on the basis of history, physical examination, endoscopic findings (presence of varices) and radiological features (ultrasonography and computed tomography). HCC was confirmed by liver biopsy. Patients who could not provide a confirmatory histopathological report of HCC were excluded from this study. Data were analyzed by SPSS (Statistical Package for Social Science) software program, version -12.

All data were presented as mean ± SD, and the distribution of data were presented in table and graphical presentation was also displayed.

RESULTS

Table I shows the baseline characteristics of patients of HCC; here, thirty (30) patients were analysed. The mean age of HCC patients was 47.8+SD14.8 years; among the patients male were 23 (76.67%) and male-female ratio was about 3.3:1. About 33.33% of the patients were farmer by occupation and others were Farmer 10 (33.33%), Business 5(16.67%), Housewife 4(13.33%), Service 3(10%), Labor 3(10%), Student 2(6.67%) and Others 3(10%). It was also found that more than 65% patient were attending the hospital from rural areas.

Table-I: Baseline characteristics of patients of HCC in Bangladesh (n=30)

Baseline characteristics of patients		30 patients
Age		
	Mean	47.8+SD14.8 years
	Range	18 - 80 years
Sex		
	Male	23 (76.67%)
	Female	7 (23.33%)
Occupation		
	Farmer	10 (33.33%)
	Business	5 (16.67%)
	Housewife	4 (13.33%)
	Service	3 (10%)
	Labor	3 (10%)
	Student	2 (6.67%)
	Others	3 (10%)

Table II states various symptoms of the patients observed during interview and from their experienced during illness. Common symptoms were loss of appetite, generalized weakness, weight loss, abdominal pain, abdominal fullness and nausea/ vomiting were noted among 29 (96.66%), 28(93.33%), 24(80%), 22(73.33%), 21(70%) and 20(66.66%) of patients respectively. Other symptoms like abdominal mass 20(66.66%), yellow coloration of eyes and urine 10(33.33%), fever 10 (33.33%), leg swelling 9(30%) abdominal swelling 9(30%), blood vomiting 1(3.33%) were also found.

Table-II: Symptoms of patients with hepatocellular carcinoma (HCC) (n=30)

Symptoms	No. of patients	Percentage
Loss of Appetite	29	96.66%
Generalized weakness	28	93.33%
Weight loss	24	80%
Abdominal pain	22	73.33%
Abdominal fullness	21	70%
Nausea/Vomiting	20	66.66%
Abdominal mass	20	66.66%
Yellow coloration of eyes & urine	10	33.33%
Fever	10	33.33%
Leg swelling	9	30%
Abdominal swelling	9	30%
Blood vomiting	1	3.33%

Table III shows the signs of HCC, here, hepatomegaly was 27(90%). Others signs were weight loss 24(80%), ascites 15(50%), splenomegaly 15(50%), jaundice 10(33.33%), testicular atrophy 10(33.33%) ans leg oedema 4 (13.33%),

Table-III: Signs of hepatocellular carcinoma (HCC) (n=30)

Sign	No. of patients	Percentage
Hepatomegaly	27	90%
Weight loss	24	80%
Ascites	15	50%
Splenomegaly	15	50%
Jaundice	10	33.33%
Testicular atrophy	10	33.33%
Palmar erythema	5	16.66%
Clubbing	4	13.33%
Oedema of legs	4	13.33%

Table IV represents the aetiological factors of HCC patients; here evidence of liver cirrhosis was found in 21(70%) of patients by ultrasonography and assessment of liver function test. Regarding etiological factors HBsAg was found in 15(50%) of patients, anti-HCV antibody was detected in 6(20%) patients, cryptogenic was 5(16.66%), autoimmune 3(10%), excessive alcoholic consumption was 1(3.33%).

Most of patients with liver cirrhosis were grouped into Child-Pugh score B (50%). Sixty percent patients had intermediate stage HCC, according to the grading of BCLC.

Table-IV: Aetiological factors of HCC patients (n=30)

Aetiological factors		No. of patients	Percentage
1.	Hepatitis B virus infection	15	50%
2.	Hepatitis C virus infection	6	20%
3.	Cryptogenic	5	16.66%
4.	Autoimmune	3	10%
5.	Alcoholic	1	3.33%

Table V shows imaging technique revealed space-occupying lesions in all patients with HCC. The number of lesions were single in 21(70%) patients and multiple in 9(30%) patients.

Table V: Ultrasonographic findings of Hepatocellular carcinoma (n=30)

	Lesion(s)	No. of patients	Percentage
Mass	Single	21	70%
	Multiple	9	30%
Echopattern	Hyperechoic	03	10%
	Hypoechoic	17	56.66%
	Mixed	10	33.33%

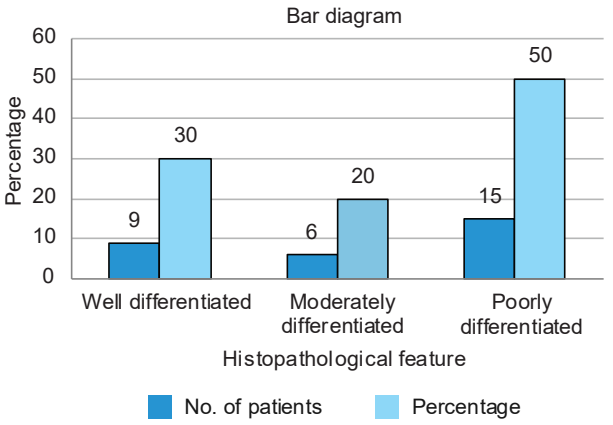

Figure-1: Bardiagram showing histopathological features of hepatocellular carcinoma (n=30)

Figure 1 illustrate the report of histopathological features after percutaneous needle biopsy, where poorly differentiated hepatocellular carcinoma were 15(50%) cases, well differentiated were 9(30%) cases and moderately differentiated were 6(20%)cases.

DISCUSSION

Hepatocellular Carcinoma is an important worldwide health issue, particularly in regions where viral hepatitis prevalence is high. This study revealed that HCC was more prevalent in males i.e, male female ratio was 3:1. Previous study conducted by Khan M et al. showed the ratio was 4:1[18], by Mohan das M et al was 3:1[21] by Shawon MA-A et al was 4:1.[22] This is due to the sex-specific differences in exposure to the risk factors, because they are more likely to be infected with HBV and HCV, as well as alcohol consumption, cigarette smoking and food habits. The liver is a hormone-sensitive organ, that's why sex hormones, such as androgen and estrogen, may be an acting factor. It is assumed that androgen promotes HCC development, whereas estrogen plays a protective role.[23-25] The typical age group affected by HCC was 50-59 and 60-69, as we have found most patients corresponded to this age group. In a study performed in Bangladesh, a group found 41 to 50 years as the most common age group to develop HCC.[26] In the United States, from the year 1992 to 2013 the age-specific incidence rate was highest in the age group of 50–69. However, a significant number of patients were also found above the age of 70.[27] The mean age of this study population was 47.8±14.8 years. The study conducted by Gani et al. (2013) comprised 57 HCC patients where the mean age was 45.81 ± 15.31 years.[28] This studt finds that chronic viral hepatitis was the major risk factor contributing to the development of HCC and HBsAg positivity was found in 15(50%) cases. This study suggests that HCC patients show a certain association between the high incidences of HBV infection. In the study by Khan M et al[18], there were 33.3% cases and by Shawon MA-A et al,[22] there were 49% cases of HBsAg positive among Bangladeshi population. Chronic HBV and HCV infection is considered as one of the leading causes of HCC in Bangladeshi population.[29-30] Despite the introduction of vaccination during 2003–2005 into the Expanded Program on Immunization (EPI) in Bangladesh, HBV infection remains abundant in the middle and older age adult population. Chronic HBV infection was the significant risk factor contributing to the development of HCC in our neighboring country India.[1] Although HCV is considered one of the leading causes of liver cancer in many countries,[32-33] in this study, HCV infection was found in 6(20%) of patients. Alcohol consumption is another risk factor of HCC in Western countries.[34-35] But this study finds that alcohol as a risk factor for underlying liver disease has contributed to only minority of patients 1 (3.3%). Alcohol consumption is strictly restricted in Bangladesh by state law and also very much restricted due to socioeconomic conditions and religious restrictions. Here, cirrhosis was found in 21(70%) cases. This study also finds the lesion of HCC at the time of diagnosis, among those single lesions were detected in 70% the cases and multiple lesions in 30% cases.[36-38] Almost all the patients in this study presented in moderate to late clinical stage of the disease. The most common presenting symptoms were loss of appetite in 29 cases (96.66%), generalized weakness in 28 cases (93.33%), weight loss 24 (80%), abdominal pain in 22 (73.33%) cases, fullness of abdomen in 21 (70%) cases, abdominal mass in 20 (66.66%) cases, nausea and vomiting 20 (66.66%) cases .Other complains were yellow coloration of eyes and urine 10 (33.33%), fever 10 (33.33%), leg swelling 9 (30%), abdominal swelling 9 (30%), blood vomiting1 (3.33%) . In previous study conducted by Khan M et al [18] the major symptoms were weight loss74%, abdominal pain 66.3%, loss of appetite78%. In Ayub Al Mamun's study common symptoms were weight loss in 94.3% cases, loss of appetite in 88.6%,abdominal mass 65.7% cases and abdominal pain in 60% cases.[39] Physical signs in this study were hepatomegaly in 27 (90%) cases, weight loss in 24 (80%), ascites 15(50%) splenomegaly 15(50%), jaundice 10 (33.33%), testicular atropy 10 (33.33%), palmer erythmia 5(16.66%), clubbing 4(13.33%), oedema of legs 4 (13.33%). Khan M et al[18] observed weight loss in 74% of patients, hepatomegaly in 66.3% cases, ascites in77.7% cases, jaundice in 37.7% cases. Histopathological features after percutaneous needle biopsy report revealed poorly differentiated hepatocellular carcinoma were 15 (50%) cases, well differentiated 9 (30%) cases and moderately differentiated 6 (20%) cases. In this study, we recorded the first clinical symptoms that have been observed while the patients were admitted in the hospitals. It was evident that every patient came with multiple clinical symptoms which were representative symptoms of HCC. The habit of Bangladeshi patients avoiding clinical checkups and regular screening of disease has become a significant influence on the development of HCC diagnosis of the disease is usually delayed. After being admitted to hospital, different imaging reports such as CT scan, MRI,

ultrasonography, biochemical tests, tumor markers, FNAC or biopsy were used for the detection of HCC.

CONCLUSION

In summary, we believe that our findings are closely representing the actual picture of hepatocellular carcinoma in Bangladeshi patients. Information regarding clinical presentation from this study may be utilized as indicator for referral, case definition in research works and probable diagnosis of HCC. This clinical presentation may be a strong tool for symptomatic surveillance of HCC and prevention of HCC including chronic hepatitis B and chronic hepatitis C virus infection. Early screening and management of chronic viral hepatitis (HBV and HCV) is needed to reduce morbidity and mortality from HCC patients. More research is required to find out clinical presentations that may lead to early diagnosis of Bangladeshi HCC patients for early and better management.

ETHICAL ISSUE

Ethical clearance for the study was taken from the Institutional Review Board of the Bangladesh college of Physicians and Surgeons (BCPS) prior to the commencement of this study (No.CPS-2007, Date-30-10-2007).

CONFLICT OF INTEREST

All authors declare that they have nothing to disclose and have no conflict of interests regarding the publication of this paper.

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Original Article

Evaluation of Serum C-Reactive Protein in Diagnosis of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis of Liver and Ascites

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Abstract

Spontaneous Bacterial Peritonitis (SBP), an infection of ascitic fluid without demonstrable intra-abdominal origin and it is a complication of cirrhosis of liver, with a reported mortality of 30% to 50% in adults. The counts of polymorphonuclear leucocytes (PMN) in ascitic fluid ≥ 250/mm² demonstrably confirms the diagnosis of SBP and the patients immediately need treatment with antibiotics irrespective of culture results. Serum C- reactive protein (CRP) is a reliable predictor of SBP and a marker that can be measured in several laboratories. The aim of this study was to estimate serum C-reactive protein levels as a diagnostic tool for evaluation of SBP in patients with liver cirrhosis and ascites. This cross-sectional study was conducted among 90 adult patients diagnosed as cirrhosis of liver with ascites in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during the period November 2017 to March 2019. Half of the patients were at their productive age (≤30 to 50 years) and others were above 50 years with mean age of 50.5 years; where male female ratio was about 2.5:1. The study found that more than one-fifth (21.1%) of the patients had SBP positive (SBP group) and their mean serum CRP was found 84.59±39.66mg/L; on the other hand rest of the patients were SBP negative (non-SBP group) with mean serum CRP was 15.02 ± 18.34 mg/L. The mean total WBC count and neutrophil count in ascitic fluid were found 2565 ± 3439/mm³ and 1255 ± 1708/mm³ in SBP patients; where 178 ± 149/mm³ and 46 ± 38/ mm³ in non-SBP patients respectively. At the serum CRP cut-off level of 41.5 mg/L, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 89.5%, 94.4%, 81% and 97.1% respectively. In the diagnosis of SBP based on PMN 2250/mm³, the accuracy of the test result was 93.3% and based on ascitic fluid culture results it was 78.9%. It is vital to assess the utility of CRP in diagnosis of SBP in cirrhosis of liver with ascites. At the optimal cut-off level of 41.5 mg/L, the serum CRP value had the good sensitivity (89.5%), specificity (94.4%), and AUC-ROC (0.969) in diagnosis of SBP. Large scale analytical studies on cirrhotic patients with ascites are encouraged to establish the optimum cut-off value of CRP for the diagnosis of SBP.

Keywords: *CRP, cirrhosis of liver, spontaneous bacterial peritonitis*

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is defined as an infection of ascitic fluid without a proven intra-abdominal source of infection.[3, 18, 25, 33] Spontaneous bacterial peritonitis (SBP) is an important cause of morbidity and mortality in cirrhosis of liver with ascites. According to studies, the prevalence of SBP in patients with cirrhosis varies from 7% to 30% per year.[1,23,29,69-88,90] In another study the prevalence of SBP in hospitalized patients with liver cirrhosis and ascites was high, ranging between 10% and 30%.[106] In-hospital mortality rates from SBP range between 30% and 50%, but a rapid detection and treatment of this disease leads to significant reduction in the mortality rate to less than 10%.[49] The typical presentation of SBP are fever and generalized abdominal pain.[45] or may lead to the development of hepatic encephalopathy and renal failure.[68] The SBP is suspected

in patients with liver cirrhosis and ascites when they present with symptoms such as acute abdominal pain, fever, and/or altered mental status. However, some patients may be asymptomatic and the SBP is detected by diagnostic paracentesis and study of the ascitic fluid after admission to the hospital for another reason like hematemesis, melena, hepatorenal syndrome and/or hepatic encephalopathy.[12,13]

Hepatic dysfunction results in impaired defenses against bacteria, and associated with structural and functional modifications in the intestinal mucosa that result in an increase in the permeability to bacteria and bacteria-derived products, which worsens over time as the disease progresses.[9]

SBP occurs when a bacterial infection spreads to the ascitic fluid through the gut wall or lymphatics but less commonly via hematogenous spread in absence of a recognized intra- abdominal source of bacterial infection or malignancy.[112] SBP is a major complication of liver cirrhosis and ascites and is considered the most frequent bacterial infection in patients with liver cirrhosis.[19]

SBP is diagnosed on the basis of ≥250 polymorphonuclear leukocytes (PMN) /mm^3 of ascitic fluid irrespective of a positive ascitic fluid culture results and an absence of intra-abdominal source of infection[100] and to begin antibiotics without waiting for culture report.[56,1,23,29,69-88,90] This valid diagnostic tool of SBP has high false negative results.[53] This procedure is operator-dependent, lysis of PMNs can occur during transport to the laboratory, and that explains the presence of false-negative results. Ascitic fluid culture is less sensitive and this conventional method detects bacteria in only 42%-65% of patients[1,23,29,69-88,90] and also time consuming. Alternative methods using automated PMN counting,[11] reagent strips (urine dipsticks),[50] or ascitic lactoferrin[53] have been developed; unfortunately, their diagnostic accuracies are limited and their use depend on availability of laboratory personnel and reagents from the commercial source.[67]

Some authors reported that serum C-reactive protein (CRP) level may also be used as an alternative test for the diagnosis of SBP. CRP is an acute phase reactant which binds to different substrates. It activates the complements, takes part in cytokine secretion, and increases the phagocytic activity of leucocytes. Serum CRP level has been reported to be a reliable predictor of SBP.[55] This marker is one of the most common clinical and inflammatory indicators that can be measured in any laboratory.[52,95] High serum levels of CRP in children with SBP were found [61] and serum CRP was a useful marker in the early detection of SBP with high sensitivity and high negative predictive value.[101] Conventional diagnosis of SBP by detecting the number of PMN in ascitic fluid is laborious and operator dependent having inter-observer variation. Serum CRP is a cheap, relatively noninvasive, simple to perform and can be measured in any laboratory. Some studies from different countries also mentioned that serum CRP had high sensitivity and specificity for early diagnosis of SBP.

MATRIALS AND METHODS

This cross-sectional study was conducted among 90 adult patients who were admitted in the Gastroenterology Department, BSMMU, Dhaka and diagnosed as cirrhosis of liver with ascites during the period November 2017 to March 2019. Ethical clearance was obtained from Institutional Review Board (IRB), BSMMU. Both written and verbal consent were taken from patients prior to enroll into the study. Diagnosis of cirrhosis was confirmed from clinical, laboratory and ultrasonographic findings. Their clinical history, examination and initial investigation report was noted in the standard data sheet. Blood samples were send for complete blood count, prothrombin time, serum creatinine, albumin, bilirubin, liver enzymes and serum CRP. Quantitative CRP was measured by the automated analyzer, Beckman Coulter-AU680. Abdominal paracentesis was done under all aseptic precautions. Laboratory analysis of the ascitic fluid was performed without delay including total and differential cell counts, total protein levels and culture sensitivity test. PMN cell count was performed by a traditional hematological method with an optical light microscope in a manual counting chamber. This method is presently considered the "gold standard" for the evaluation of ascitic fluid PMN count (Riggio *et al.*, 2009). Ten (10) ml of ascitic fluid sample was inoculated in blood culture bottles at bedside for culture and sensitivity test. Diagnosis of SBP was based on PMN cell count ≥250/mm^3 in ascitic fluid irrespective of a positive ascitic fluid culture result. The values of serum CRP were compared with asctic fluid PMN count, ascitic fluid culture results and both. All the tests were done at department of biochemistry, department of clinical pathology and department of microbiology of BSMMU, Dhaka, Bangladesh.

Data processing and analysis:

Statistical analysis of the results being obtained by using windows based computer software devised with Statistical

Packages for Social Sciences (SPSS) version 22. After compilation, data were presented in the form of tables, figures and charts, as necessary. Numerical variables were expressed as mean and standard deviation, whereas categorical variables were counted with perc Categorical variables were analyzed by Chi-squa Significance of CRP in SBP was done by Mann Whi test. Fisher's exact test was done for significance of among SBP patients. Validity test was done to calcul diagnostic utility of CRP in diagnosing SBP. P value than 0.05 was considered statistically significant.

RESULTS

This cross-sectional study was conducted in the Department of Gastroenterology, BSMMU, Dhaka, from November 2017 to March 2019. A total of 90 cirrhotic patients with ascites were included in this study.

Table I shows age-group distribution of patients with cirrhosis of liver and ascites, it was observed that 30% of the patients belongs to age 51-60 years, the mean age of patients was 50.5 years with SD of ±14.3 years. The age range of the patient was from 19 to 95 years.

Table- I: Distribution of the study patients according to age group (n=90)

Age (years)	Frequency (n)	Percentage (%)
≤30	8	8.9
31 - 40	18	20.0
41 - 50	19	21.1
51 - 60	27	30.0
>60	18	20.0
Mean ± SD (years) (Age range)	50.5 ± 14.3(19-95)	

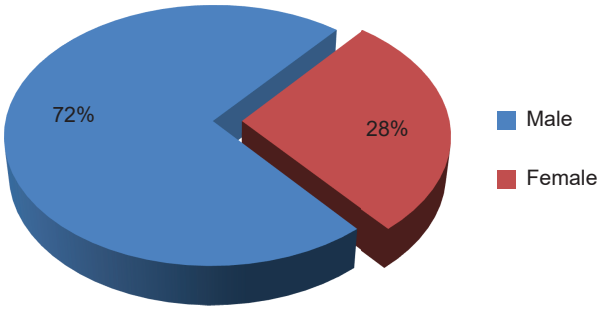

Figure 1: Pie chart showing sex distribution of the patients.

Figure- 1 illastrates the distribution of sex of the patients, it was observed that 72% of theme were male and the male female ratio was about 2.5:1.

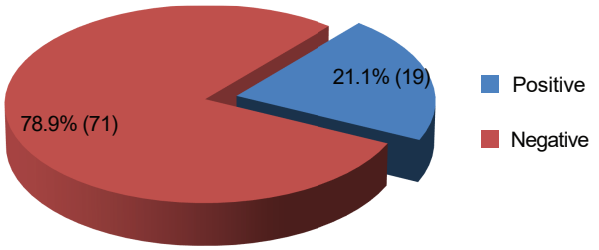

Figure 2: Pie chart showing distribution of patients with SBP positive and negative cases.

Figure- 2 shows the distribution of patients with SBP, among the patients, it was observed that 21.1% of the patients were SBP positive.

Table II shows presenting complaints of SBP patients. It was observed that 15(78.9%) had fever, 15(78.9%) had abdominal pain, 3(15.8%) SBP patients were presented with altered level of consciousness, one (5.3%) presented with haematemesis and 3(15.8) were presented with melena and 10.6% had SBP without any symptom.

Table- II: Presenting complaints of the SBP patients (n=19)

Presenting illness	Spontaneous bacterial peritonitis (SBP) Positive (n=19)
Fever	15 (78.9%)
Abdominal pain	15 (78.9%)
Altered level of consciousness	3 (15.8%)
Haematemesis	1 (5.3%)
Malaena	3 (15.8%)
Asymptomatic	2 (10.6%)

Table- III states the distribution of underlying causes of cirrhosis among the patients, 68.9% of the patient were related to chronic hepatitis B virus infection. Among the positive cases of SBP 15 (78.9%) and among the negative cases 47(66.2%) had had chronic hepatitis B virus infection. Among the patients 10 (11.1%) were related to chronic hepatitis C infection and none them had SBP.

Table III: Underlying cause of cirrhosis of liver of the study subjects (n=90)

	Spontaneous bacterial peritonitis (SBP)	
Causes of cirrhosis	Positive (n=19) (%)	Negative (n=71) (%)
HBV	15 (78.9)	47 (66.2)
HCV	0 (0.0)	10 (14.1)
Wilson's disease	0 (0.0)	1 (1.4)
NASH	0 (0.0)	1 (1.4)
Cryptogenic	4 (21.1)	12 (16.9)

Table IV shows clinical examination findings of the study patients, it was observed that 16 (84.2%) patients in SBP group and 59 (83.1%) in non-SBP group had anemia. There were 14 (73.3%) patients in SBP group and 53 (74.6%) patients in non-SBP group had leukonychia. There were 14 (73.7%) patients in SBP group and 44 (62.0%) patients in non-SBP group had palmar erythema. Other findings are shown in the table below.

Table IV: Clinical examination findings of the study patients (n=90)

General examination	Spontaneous bacterial peritonitis (SBP)		
	Positive (n=19)	Negative (n=71)	p-value
Anaemia	16 (84.2)	59 (83.1)	1.000#
Jaundice	7 (36.8)	16 (22.5)	0.241#
Leukonychia	14 (73.7)	53 (74.6)	1.000#
Clubbing	1 (5.3)	0 (0.0)	0.211#
Palmar erythema	14 (73.7)	44 (62.0)	0.343*
Spider	7 (36.8)	12 (16.9)	0.119#
Gynaecomastia	7 (36.8)	29 (40.8)	0.752*
Oedema	5 (26.3)	20 (28.2)	0.873*
Palpable liver	2 (10.5)	5 (7.0)	0.636#
Palpable spleen	5 (26.3)	25 (35.2)	0.465*
Testicular atrophy (male)	12 (75.0)	29 (40.8)	0.255*

*Chi-square test and #Fisher's Exact test was done to measure the level of significance

Table VI shows the culture result of the ascitic fluid of the study patients. There were 19 patients with SBP among them 2(10.5%) patients were culture positive and 17(89.5%) patients with SBP were culture negative. Of the two patients with culture positive SBP, one was *E. coli* and another was positive for *Klebsiella species*. The culture results were significant among the SBP patients (p=0.043).

Table- VI: Spontaneous bacterial peritonitis (SBP) according to ascitic fluid culture report (n=90)

Culture	Spontaneous bacterial peritonitis (SBP)		
	Positive (n=19) (%)	Negative (n=71) (%)	p-value
Positive	2 (10.5)	0 (0.0)	0.043s
Negative	17 (89.5)	71 (100.0)	

s= significant
Fisher's Exact test was done to measure the level of significance

Table VII shows the sensitivity and specificity of CRP at different level. At a cut-off value of 41.5 mg/L, the serum CRP value had optimal sensitivity of 89.5% and optimal specificity of 94.4% and the Youden's Index was 0.83. In this study patients had taken serum CRP of 41.5 mg/L as cut-off value.

Table- VII: Sensitivity and specificity of CRP at different serum level diagnosis of SBP in study patients (n=90)

Serum CRP (mg/L)	Sensitivity (%)	Specificity (%)	Youden's Index
36.34	89.5	85.9	0.754
37.24	89.5	87.3	0.768
37.90	89.5	88.7	0.782
38.40	89.5	90.1	0.796
39.90	89.5	93.0	0.824
41.50	**89.5**	**94.4**	**0.838**
44.29	84.2	94.4	0.786
48.42	84.2	95.8	0.800

Table VIII shows the validity test results of serum CRP at a cut off level of 41.5 mg/L in the diagnosis of SBP by ascitic fluid PMN count, which shows the sensitivity of 89.5%, specificity of 94.4%. The positive predictive value was 81% and negative predictive value was 97.1%. The accuracy of the test result was 93.3%.

Table- VIII: Validity test of CRP at a cut off value of 41.5 mg/L in diagnosis of SBP by ascitic fluid PMN count in study patients (n=90)

Validity Indices	%	95% CI	
		Min	Max
Sensitivity	89.5	70.5	98.0
Specificity	94.4	89.3	96.6
PPV	81.0	63.8	88.6
NPV	97.1	91.9	99.4
Accuracy	93.3	85.3	96.9

PPV= Positive Predictive Value
NPV= Negative Predictive Value

Table IX shows the validity test results of serum CRP at a cut-off level of 41.5 mg/L in the diagnosis of SBP by ascitic fluid culture, which shows the sensitivity of 100%, specificity of 78.4%. The positive predictive value was 9.5% and negative predictive value was 100%. The accuracy of the test result was 78.9%.

Table- IX: Validity test of CRP at a cut off value of 41.5 mg/L in diagnosis of SBP by ascitic fluid culture in study patients (n=90)

Validity Indices	%	95% CI	
		Min	Max
Sensitivity	100.0	20.1	100.0
Specificity	78.4	76.6	78.4
PPV	9.5	1.9	9.5
NPV	100.0	97.7	100.0
Accuracy	78.9	75.3	78.9

PPV= Positive Predictive Value
NPV= Negative Predictive Value

Table X shows the validity test results of serum CRP at cut-off level of 41.5 mg/L in the diagnosis of SBP by both ascitic fluid culture and PMN count, which shows the sensitivity of 89.5%, specificity of 94.4%. The positive predictive value was 81% and negative predictive value was 97.1%. The accuracy of the test result was 93.3%.

Tabl-X: Validity test of CRP at a cut off value of 41.5 mg/L in diagnosis of spontaneous bacterial peritonitis (by both ascitic fluid culture and PMN count) in study patients. (n=90)

Validity Indices	%	95% CI	
		Min	Max
Sensitivity	89.5	70.5	98.0
Specificity	94.4	89.3	96.6
PPV	81.0	63.8	88.6
NPV	97.1	91.9	99.4
Accuracy	93.3	85.3	96.9

PPV= Positive Predictive Value
NPV= Negative Predictive Value

ROC (Receiver Operating Characteristic) curve:

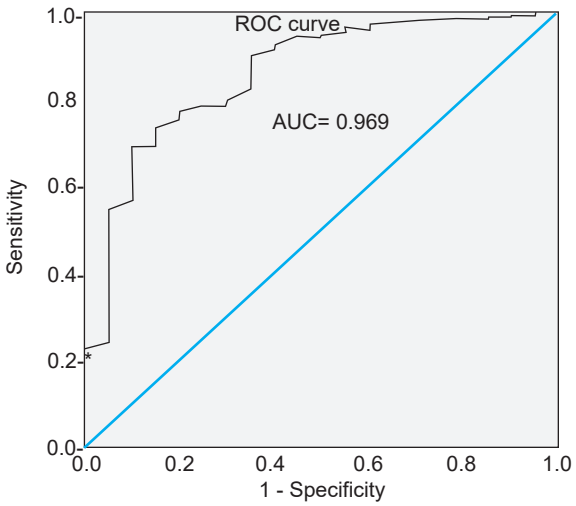

Figure 3: Area under ROC curve showing 0.969 with 95% CI, (0.909-1.000), (P <0.001).

Figure- 3 shows the ROC curve was generated by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) at different cut-off points. The figure shows AUC score of 0.969, which is close to 1. It indicates that serum CRP at a cut-off level of 41.5 mg/L have higher accuracy in diagnosing SBP in the study patients with high significance (p-value <0.001).

DISCUSSION

This cross-sectional study enrolled 90 patients with cirrhosis of liver and ascites; among the patients, 19 patients had SBP according to ascitic fluid PMN count ≥

250/mm^3. The most common clinical presentation was fever and abdominal pain (each 78.9%), altered mental status (15.8%), upper GIT bleeding (21.1%) while 10.6% of patients were asymptomatic. These results were consistent with the study conducted by [1,23,29,69-88,90] in which fever was the most common presenting feature (67%), followed by abdominal pain (60%), abdominal tenderness (42%) and encephalopathy (57%). Bandy and Tuttle, in 2008 reported that as many as 30% of patients with paracentesis-proven SBP may be completely asymptomatic.

The finding of ascitic fluid protein concentration in SBP patients were almost similar to that reported by.[98] They have found mean ascitic fluid protein 9.3± 4.4gm/l, whereas this study found mean ascitic fluid protein 10.97±04.04gm/L in SBP patients. Ascitic fluid analysis in study patients at admission by Syed *et al.* 2007 showed that, the mean ascitic fluid protein was slightly higher in non-SBP group than SBP group (12± 7.5gm/l vs 11±7.2gm/l). In this study the mean ascitic fluid protein in patient of non- SBP group was also higher than SBP group (13.25 ± 5.62 gm/L vs 10.97 ± 4.04gm/L). It may be due to the difference in immune status as well as etiology of cirrhosis in patients (due to HBV and HCV infection), compared to other studies (alcoholic cirrhosis). Runyon, B.A, (1986) had demonstrated that cirrhotic patients with ascitic protein concentrations below 1 g/dl were 10 times more likely to develop SBP than individuals with higher concentration.

Conventional diagnosis of SBP by detecting the number of PMN in ascitic fluid is laborious and operator dependent having inter-observer variation. It is not available everywhere especially in small hospitals with poor laboratory facilities,[66,39,41,42] implied that serum CRP determination can be used to detect bacterial infection in liver cirrhosis patients; Tsiakalos *et al.* (2009) found that CRP, ferritin and β2-microglobulin, significantly increased when cirrhotic patients are affected by bacterial infections, irrespective of the underlying cause of cirrhosis. Our results do suggest that measurement of serum CRP may be useful for excluding the possibility SBP in cirrhotic patients.

The serum CRP level in cirrhosis with ascites seems to be a reliable test to identify SBP, because our study showed the statistically significant difference of its levels between the SBP group and non-SBP group; as mean CRP level 84.59mg/L vs 15.02mg/L (P<0.001), as well as its high diagnostic sensitivity, specificity and accuracy (89.5%, 94.4%, and 93.3% respectively) at a cut-off level of 41.5mg/L. These finding are similar to that of several other previous studies.[8,52,95] The increase in the CRP levels can be partially attributed to its independent production regulation by interleukin-6 and its insensitivity to hepatocyte growth factor[24] or by other cell types such as alveolar [9,16,115] and renal cells.[32] The contrast result was explained by, Le Moine *et al.* in 1994 found CRP to have weak predictive power for infection in patients with decompensated cirrhosis but the production of CRP is reduced, but not abolished, even in patients with advanced liver [52,95]

In this study, at a cut-off value of 41.5mg/L the serum CRP level showed 89.5% sensitivity, 94.4% specificity, 81% PPV, 97.1% NPV and accuracy of 93.3% for detecting SBP. No significant difference was observed between PMN count and both PMN and culture results in terms of diagnostic efficacy of CRP. But sensitivity, specificity, PPV, NPV and diagnostic accuracy of serum CRP in diagnosing SBP based on ascitic fluid culture results were 100%, 78.4%, 9.5%, 100% and 78.9% respectively, with low specificity, PPV and accuracy when compared with PMN alone or with both PMN and culture results. Study conducted on 150 cirrhotic patients with ascites showed 88.43% sensitivity, 84.32% specificity, 85.48% PPV, 90.32% NPV and 85.63% accuracy of serum CRP in diagnosing SBP when compared with ascitic fluid culture[34]. This may be due to large sample size, more culture positivity among study subjects and the use of higher cut-off level of serum CRP.

There are variable cut-off level of CRP level in different previous studies[67] had shown that at a cut-off value of 30 mg/dl, the serum CRP was 96% specific and 90% sensitive for detecting SBP[39,41,42], at a cut-off value of 20 mg/L, the serum CRP had sensitivity of 80.39%, specificity of 80.77% and accuracy of 80.62%). Likewise, the optimal diagnostic cut-off value of CRP was 16.15 mg/L in chronic severe hepatitis B patients with SBP, with sensitivity of 64% and specificity of 95% [26,114] and optimal cut-off value of CRP that can be used for the diagnosis was 10.5 mg/L with sensitivity and specifity of 91% and 97% respectively.[103] Therefore, it is necessary to find a new cut-off value to discriminate infection as well as SBP in patients of cirrhosis with ascites. Study had suggested that the threshold should be moved to 55.8 mg/L, because above these levels, it has almost the similar sensitivity (79%), but much better specificity (96%) and diagnostic accuracy (92%)[103].

CONCLUSION

It is vital to assess the utility of CRP in diagnosis of SBP in cirrhosis with ascites. In previous clinical studies, CRP proved to be effective marker of bacterial infections in patients with liver diseases, but they had diverse diagnostic accuracies at different cut-off values. In this study, CRP at the optimal cut-off value at 41.5 mg/L had the good sensitivity (89.5%), specificity (94.4%), and AUROC (0.969) in diagnosing SBP patients. Larger samples and more homogeneous groups of cirrhotic patients with SBP is need for further studies in order to confirm our results and to establish the optimal cut-off level of CRP for the diagnosis of SBP.

Limitation

The sample size of the study was small.

All patients were collected in this study from a single tertiary level hospital which does not reflect the whole country so, current study suffered from lack of multi-centric patients.

Recommendation

There is a need of large sample study.

The optimal cutoff level of CRP needs to be reached from an independent cohort of patients with SBP.

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Original Article

Bacteriological Etiology of Empyema Thoracis Patients Admitted in a Tertiary Care Hospital

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Abstract

Empyema thoracis is the most common complication of pneumonia and is associated with severe morbidity and mortality. Management of empyema thoracis is complex and needs a multimodal approach. Antibiotic therapy is very crucial in management of empyema thoracis and epidemiological data is essential to ensure appropriate antibiotic therapy. This study aimed to explore the bacteriological profile of empyema thoracis in a tertiary care hospital. This cross-sectional study was carried on 30 patients admitted in the Department of Medicine and Department of Respiratory Medicine, Sir Salimullah Medical College and Mitford Hospital (SSMC & MH), Dhaka over a period of six months (March to September 2021). Mean age of the patients was 38±10.94 (SD) years and male–female ratio was 2:1 (66.7% male). The most common symptoms were found cough (86.7%) and fever (83.3%) including major presenting symptoms expectoration (76.7%) and chest pain (70.0%); other symptoms were loss of appetite (50.0%), malaise (46.7%) and hemoptysis (10.0%). The major etiology was the thoracic empyema (56.7%) followed by pneumonia (16.67%), lung abscess (10.0%), liver abscess (6.7%), lung cancer (3.3%), secondary infection (3.3%) and undetermined cases responding to antibiotics (3.3%). Bacteriological profile showed that majority of the cases (56.7%) were Mycobacterium Tuberculosis; others cases were S. aureus (6.7%), S. pyogen (6.7%), E. coli (3.3%), Klebsiella (3.3%) and Pseudomonas (6.7%). It was concluded from the study, more than half of empyema thoracis was etiologically tubercular.

Keywords: *Empyema thoracis, bacteriological profile, tuberculosis*

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INTRODUCTION

Among thoracic diseases, Empyema thoracis (ET) is one of the common which is more prevalent in developing countries. This is an inflammatory process of infection in a pleural cavity where the purulent material accumulates and organizes in that cavity.[1] Parapneumonic effusion following bacterial pneumonia is the most common precursor of empyema.[2] ET incidence is steadily rising even with the advancements in the antibiotic treatment era. Mortality and morbidity vary between 3% and 33%.[3, 5] Around the globe, the incidence and prevalence of empyema have been increasing both among the pediatric and adult age groups. The causative bacteria are also changing. In 2013, there were 7.15 cases per 100000 inhabitants which increased to 7.75 cases per 100000 inhabitants in 2017. Empyema patients have mortality and surgery rates remained consistent at around 14%.[6] Each year in the UK and USA, over 65000 patients suffer from pleural infection. Approximately 15% of these patients die and another 30% require surgical drainage of the pleural space.[7] The pathophysiology of ET is a gradual process. According to the American Thoracic Society, the ET has three phases: (1) exudative (acute or Stage I), where exudative fluid accumulates without loculation; (2) fibrinopurulent (Stage II), where pleural fluid becomes turbid or purulent with loculation; and (3) organizing (chronic or Stage III), where thickened pus or fibrin peels start to form, and the pleural space start to replace by granulation tissue.[8,9] There are varieties of etiological factors for ET including bacteria, fungi, and amoebas, in association with pneumonia. Other causes include penetrating chest trauma, thoracic surgery, and esophageal rupture.[2] Among pediatric population, over 50% of ET cases are due to Streptococcus pneumoniae. In case of

adult patients, microorganisms varied significantly over time. During pre-antibiotic era, Streptococcus pneumoniae accounted for majority of cases, Streptococcus pyogenes and Streptococcus aureus were prevalent as well.[7] Clinical manifestations of empyema vary with anatomical location of infection and level of severity.[10] Common clinical features of ET are broad-spectrum and like that of bacterial pneumonia. Patients generally present with fever, fatigue, cough, shortness of breath and chest pain. Infections with anaerobes tend to lead a more insidious clinical course with less pronounced fever and more generalized systemic symptoms, such as poor appetite and weight loss.[11,12] The management of empyema can be challenging and complex. Coordination of care across multiple disciplines is necessary, functioning as a cohesive interprofessional team, to optimize positive patient outcomes. Since therapeutic options for empyema involve medical and surgical intervention, the involvement of several specialists is prudent in improving morbidity and mortality. Appropriate empiric antibiotic therapy for acute pleural empyema incorporates an understanding of the patient's clinical history, local antimicrobial resistance patterns, institutional antibiotic stewardship, and pharmacologic characteristics of the antibiotics. The best course of treatment is debatable, especially when it comes to the length of parenteral antibiotics and the importance of surgery. The current management of empyema is highly diverse, owing to a variety of clinical presentations and provider experiences. The bacteriological etiology of empyema thoracis, as well as antibiotic sensitivity, will aid us in developing a suitable treatment plan.[10,13]. Considering this, the aim of the study was to assess the bacteriological etiology of patients of empyema thoracis admitted in a tertiary care hospital.

MATERIALS AND METHODS

This cross-sectional study was conducted in 30 adult (age>18 years) patients of Empyema thoracis admitted in the Department of Medicine and Respiratory Medicine, Sir Salimullah Medical College and Mitford Hospital, Dhaka from March to September 2021. After arrival of patient of suspected empyema thoracis, detailed history was taken from the patient and examined thoroughly. After initial chest radiograph pus from pleural space was aspirated according to indication and pleural aspirate was investigated for cytology, biochemistry, protein, sugar, Gram staining and culture sensitivity and Acid-Fast Bacilli staining. A total of 30 patients with confirmed empyema thoracis (pleural fluid demonstrated on chest radiograph that contained > 1000 WBC/mm^3 from which organism could be cultured[14]) were included in this study. Patients who developed post surgical or post traumatic empyema as well as pregnant and lactating mother were excluded from this study. Written consent was taken from all the patients after informing the necessary information's regarding the research study. Then necessary data were collected in a preformed questionnaire.

STATISTICAL ANALYSIS:

After collection, data were checked for consistency and completeness and were cleaned and edited. Statistical Package for Social Sciences (SPSS) 23 was used to analyze the data. Data were presented by tables, diagram, percentage chart etc. The frequency rates of various information were described and compared by using statistical method.

RESULTS

In this study a total 30 cases were included who had confirmed Empyema thoracis fulfilling clinical, radiological, biochemical and microbiological criteria. Out of them 20 (66.7%) were male and rest (33.3%) were female; male-female ratio was 2:1. The mean age for the study population was 38±10.94 (SD) years. In age distribution 33.3% was in age group18-30 years; 26.7% of population had in each age group of 31-40 years and 41-50 years, where 10% were in age group 51-60 years and only 3.3% were in more than 61 years of age group.

Among the respondents 30.0% completed their primary education, 6.7% completed their graduation. Among all, 27.0% were housewives, 17.0% were farmer, 17.0% were unemployed or retired, students were 13.0%, 13.0% were labour and 13.0% were in service. Considering economic status 60.0% of the respondents belonged to middle income family whereas 23.0% were from a poor family and 17.0% were from rich family.

Table I shows the distribution of symptoms of the patients, here cough, fever, expectoration, weight loss, chest pain, dyspnea, loss of appetite, malaise and hemoptysis were present in 86.7(%), 83.3(%), 73.33 (%), 76.7 (%), 70.0 (%), 63.3 (%), 50.0 (%), 46.7 (%) and 10.0 (%) of patients respectively.

Table I: Distribution of the patients by the symptoms (n=30)

Symptoms*	Frequency (n)	Percentage
Fever	25	83.3 (%)
Cough	26	86.7 (%)
Chest pain	21	70.0 (%)
Weight loss	22	73.33 (%)
Expectoration	23	76.7 (%)
Dyspnea	19	63.3 (%)
Hemoptysis	3	10.0 (%)
Malaise	14	46.7 (%)
Loss of appetite	15	50.0 (%)

*Multiple responses considered

Table II contains the distribution of etiology of empyema thoracis of the patients; here tubercular causes was 56.67 (%) and Non-tubercular causes were 43.33% (lung abscess, lung cancer, pneumonia, liver abscess, secondary infection and undetermined cases responding to antibiotics were 10.0 %, 3.3%, 16.67 %, 6.7%, 3.3% and 3.3% respectively).

Table-II: Distribution of study patients by the etiology (n=30)

Etiology	Frequency (n)	Percentage
Tubercular causes	17	56.67 (%)
Non-tubercular causes	13	43.33(%)
Lung abscess	3	10.0 (%)
Lung cancer	1	3.3 (%)
Pneumonia	5	16.67 (%)
Liver abscess	2	6.7 (%)
Secondary infection	1	3.3 (%)
Undetermined cases responding to antibiotics	1	3.3 (%)

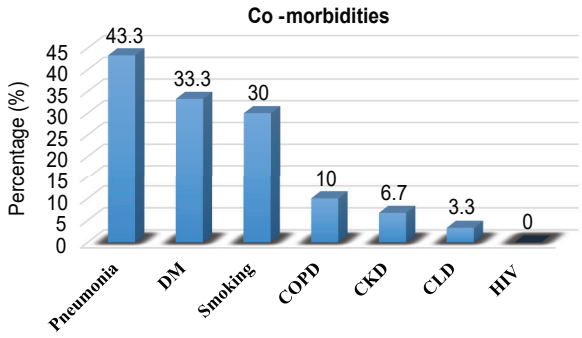

Figure-1: Distribution of the patients by the co-morbidities and risk factors (n=30)

Figure 1 represents the distribution of the patients by the co-morbidities and risk factors; here co-morbidities were detected in 96.6% of patients among them pneumonia, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), chronic liver disease (CLD), human immunodeficiency virus (HIV) were found in 43.3%, 33.3%, 10%, 6.7%, 3.3% and 00% respectively. Other 3.4% had no co-morbidities. Out of total patients 30% were smokers.

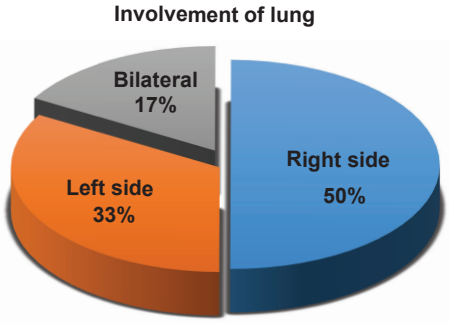

Figure- 2: Distribution of the patients by the involvement of lungs (n=30)

Figure 2 shows the distribution of the respondents by the involvement of lungs; where right lung was involved in 50% of the patients, left lung 33% and both lungs 17%.

Table III states the distribution of laboratory reports with the reference range of parameters of the patients; here table contains the parameters of Hb (gm/dl), WBC (Total count) (in ells/mm3), WBC (differential Count), Neutrophil (%), Lymphocyte (%), RBS (mg/dl), S.creatinine, S.Bilirubin (mg/dl), Urea (mg/dl), ESR (in mm 1st hour) and Mean±SD (counts or blood level) of parameters were 9.49±2.86, 8423.33±4444.27, 82.9±6.6, 8.1±5.1, 152.30±96.21, 0.93±0.40, 0.61±0.26, 22.83± 14.29, 64.83±25.31 respectively.

Table- III: Laboratory parameters of the study patients (n=30)

Parameter	Mean±SD	Range
Hb (gm/dl)	9.49±2.86	4.50-14.0
WBC (Total count) (in cells/mm3)	8423.33±4444.27	1400-22000
WBC (differential Count)		
Neutrophil (%)	82.9±6.6	75.0-90.0
Lymphocyte (%)	8.1±5.1	3-13.0
RBS (mg/dl)	152.30±96.21	24-510
S.creatinine	0.93±0.40	0.30-1.80
S. Bilirubin (mg/dl)	0.61±0.26	0.10-1.0
Urea (mg/dl)	22.83±14.29	10-60
ESR (in mm 1st hour)	64.83±25.31	20.00-105.00

Table IV delineates the name of organisms that were identified from the patients' of empyema thoracis; Mycobacterium Tuberculosis (MTB) were identified in 17 (56.7%) patients. Gram (+) ve bacteria like *staphylococcus aureus (S. Aureus)* and *streptococcus pyogens (S. Pyogens)* were found in both of each 2 (6.7%) of patients. Gram (-) ve bacteria- *Pseudomonus and Klebsiella* were detected from 2 (6.7%) and 1 (3.3%) of patients respectively. *Escherichia coli (E. coli) and Polymicrobials were* identified in both of each 1 (3.3%) of patient. Sterile patients were found 4(13.3%).

Table-IV: Distribution of the patients by identified organisms (n=30)

Organisms identified in this study	**Frequency (n)**	**Percentage**
Mycobacterium Tuberculosis (MTB) Gram (+)ve	17	56.7
Staphylococcus aureus (S. Aureus)	2	6.7
Streptococcus pyogens (S. Pyogens) Gram (-) ve	2	6.7
Pseudomonus	2	6.7
Klebsiella	1	3.3
Escherichia coli (E. coli)	1	3.3
Polymicrobials	1	3.3
Sterile	4	13.3

Table V describes the pleural fluid analysis of the study patients; regarding pleural fluid analysis, total WBC count was 6843.33±11831.01 (SD) (in cells/mm3), neutrophil count was 5326.67±11207.29 (SD) (in cells/mm3), lymphocyte count was 795.10±947.00 (SD) (in cells/mm3), protein was 3.79±0.81 (SD) mg/dl and sugar was 61.06±41.15 (SD) mg/dl.

Table-V: Pleural fluid analysis of the study patients (n=30)

Parameter	Mean±SD	Range
WBC (Total count) (in cells/mm^3)	6843.33± 11831.01	400-67400
Neutrophil (in cells/mm^3)	5326.67± 11207.29	300-64010
Lymphocyte (in cells/mm^3)	795.10± 947.00	30-4000
Protein (gm/dl)	3.79±0.81	3.00-5.60
Sugar (mg/dl)	61.06±41.15	25-189

Table VI and Table VII depicts the distribution of the study patients by the antibiotic sensitivity and resistance to the organism isolated. Antibiotic sensitivity of the isolated organisms from patients are depicted in ciprofloxacin was sensitive to 13.3% gram (+) ve and 33.3% gram (-) ve organism whereas it was resistant to 6.7% gm (+) ve and 46.7% gm (-) ve organisms. Gentamicin was sensitive to 33.3% gm (+) ve and 26.7% gm (-) ve organisms whereas resistant to 40.0% gm (-) ve organisms. Ceftazidime was sensitive to 33.3% gm (+) ve and 30.0% gm (-) ve organisms whereas resistant to 36.7% gm (-) ve organisms. Amikacin was sensitive to 26.5% gm (+) ve and 16.7% gram (-) ve organisms whereas resistant to 56.7% gram (-) ve organisms. Aztreonam was sensitive to 33.3% gm (+) ve and 36.7% gram (-) ve organisms whereas resistant to 30.0% gram (-) ve organisms. Meropenem was sensitive to 20.0% gm (+) ve and 56.7% gram (-) ve organisms whereas resistant to 23.3% gram (-) ve organisms. Netilmicin was sensitive to 16.7% gm (+) ve and 56.7% gram (-) ve organisms whereas resistant to 26.7% gram (-) ve organisms. Cefepime was sensitive to 26.7% gm (+) ve and 46.7% gram (-) ve organisms whereas resistant to 26.7% gram (-) ve organisms. Celestin sulphate was sensitive to 26.7% gm (+) ve and 73.3% gram (-) ve organisms. Tazobactam+Piperacillin was sensitive to 16.7% gm (+) ve and 20.0% gram (-) ve organisms whereas resistant to 3.3% gram (+) ve and 20.0% gram (-) ve organisms.

Table- VI: Distribution of the study patients by the antibiotic sensitivity and resistance to the organism isolated (n=30)

Name of antibiotics	Gram (+)ve		Gram (-) ve	
	Resistant N(%)	Sensitive N(%)	Resistant N(%)	Sensitive N(%)
Ciprofloxacin	2(6.7)	4(13.3)	14(46.7)	10(33.3)
Gentamicin	0(0.0)	10(33.3)	12(40.0)	8(26.7)
Ceftazidime	0(0.0)	10(33.3)	11(36.7)	9(30.0)
Amikacin	0(0.0)	8(26.5)	17(56.7)	5(16.7)
Aztreonam	0(0.0)	10(33.3)	9(30.0)	11(36.7)
Meropenem	0(0.0)	6(20.0)	7(23.3)	17(56.7)
Netelmicin	0(0.0)	5(16.7)	8(26.7)	17(56.7)
Cefepime	0(0.0)	8(26.7)	8(26.7)	14(46.7)
Colistin sulphate	0(0.0)	8(26.7)	0(0.0)	22(73.3)
Tazobactam+Piperacillin	1(3.3)	5(16.7)	6(20.0)	18(60.0)

Table VII: Distribution of the studied patients by the organism based antibiotic sensitivity (n=30)

Name of antibiotics	Name of Organisms with sensitive (%) to corresponding antibiotics					
	S. Aureus	S. Pyogens	E. Coli	Klebsiella	Pseudomonas	MTB
Ciprofloxacin	50%	75%	42.86%	28.57%	50%	100%
Gentamicin	100%	100%	42.86%	37.5%	40.0%	100%
Ceftazidime	100%	100%	66.67%	28.57%	42.86%	100%
Amikacin	100%	100%	25%	16.67%	25%	100%
Aztreonam	100%	100%	60%	50%	57.14%	100%
Meropenem	100%	100%	62.5%	80%	66.67%	100%
Netelmicin	100%	100%	42.86%	77.78%	77.78%	100%
Cefepime	100%	100%	57.14%	60%	70%	100%
Colistin sulphate	100%	100%	100%	100%	100%	100%
Tazobactam+Piperacillin	75%	100%	75%	71.43%	80%	100%

Among the isolated gram (+)ve organisms, S. Aureus showed sensitivity to Gentamicin, Ceftazidime, Amikacin, Aztreonam, Meropenem, Netelmicin, Cefepime and Colistin sulphate. S. Pyogens showed sensitivity to Gentamicin, Ceftazidime, Amikacin, Aztreonam, Meropenem, Netelmicin, Cefepime, Colistin sulphate and Tazobactam+Piperacillin. Besides, among the isolated gram (-)ve organisms, E.Coli showed sensitivity to Colistin sulphate (100%) followed by Tazobactam+Piperacillin (75%), Ceftazidime (66.67%) and Meropenem (62.5%). Klebsiella showed sensitivity to Colistin sulphate (100%) followed by Meropenem (80%) and Netelmicin (77.78%). Pseudomonas showed sensitivity to Colistin sulphate (100%) followed by Tazobactam+Piperacillin (80%) and Netelmicin (77.78%). MTB showed sensitivity (100%) to all the antibiotics.

DISCUSSION

Empyema Thoracic is an infectious disease that causes the accumulation of frank pus in the pleural space of the lungs.[15] It mostly appears as a complication of hospital and community-acquired pneumonia, however, it also occurs due to other causes like thoracic injuries, chest trauma, bronchogenic carcinoma, esophageal rupture, immune-compromised status, and other post-surgical infections.[2,15] The clinical signs and symptoms of empyema include pleuritic chest pain, cough, fever, chills, weight loss, anorexia, dyspnea, and night sweats.[15,16] The diagnosis of empyema is established by the presence of pus and fluid in the pleural space followed by microbiological assay of pleural fluid while gene expert and acid-fast bacilli smear examination are used for the detection of Mycobacterium

Tuberculosis.[2] The major aim of empyema treatment is to eliminate the infection and re-expansion of lungs which is usually achieved by eradicating the bacterial growth from the pleural fluid by the use of appropriate antibiotic therapy along with the drainage process.[2,15-17] So this study aimed to assess the bacteriological etiology of empyema thoracis of patients admitted in a tertiary care hospital in Bangladesh.

Among 30 patients of this study, 1/3 rd of the patients were between 18-30 years of age group with mean age 38±10.94(SD) years. Male patients predominated over female patients with a male to female ratio of 2:1. Another similar study found that among 110 patients of empyema, the age varied from 8-74 years of age where 78.2% of the patients were between 11-50 years of age and 7.3% were less than 10 years of age. Male was also predominated over female in this study.[18] Another similar study showed male predominance with mean age 42.07±18.28(SD).[19] Majority of the patients with thoracic empyema were young and middle-aged adults. This age group represents the most productive years of life and the socio-economic impact is thus tremendous. The high incidence in this age-gender group is attributed to the predilection of pulmonary tuberculosis and community acquired pneumonia in this age gender group.[20,21]

According to this study, two-thirds of the thoracic empyema was due to tubercular causes. Among the non-tubercular causes, 16.67% were due to pneumonia, followed in decreasing order lung abscess (10.0%), liver abscess (6.7%), lung cancer (3.3%), secondary infection (3.3%) and undetermined cases responding to antibiotics (3.3%). Among the western world causes like community-acquired pneumonia, lung abscesses and surgical trauma are the commonest causes of empyema whereas among the south Asian country tuberculosis is one of the most common causes of empyema thoracis.[22-24]

The most common symptoms were cough and cough was among 86.7% of the study population of this study followed in decreasing order fever (83.3%), expectoration (76.7%), chest pain (70.0%), loss of appetite (50.0%), malaise (46.7%) and hemoptysis (10.0%). Gajendra Vikram Singh et al., and Malhotra et al., also reported almost the same.[24,25] The clinical manifestations of an empyema can vary widely, depending on both the nature of the infecting organism and the competence of the patient's immune system. The spectrum ranges from an almost complete absence of symptoms to a severe illness with systemic toxicity. In general, anaerobic and tubercular empyema usually present with a sub-acute illness, whereas aerobic bacterial infections of the pleural space present with an acute illness.[24]

Regarding co-morbidities and risk factors, H/o pneumonia was among 43.30% of the study population, DM was among 33.30% of the patients, 30% patients had H/o smoking, besides 10% patients had COPD. A similar study in India showed pneumonia as the most common co-morbidities which was among 41% of the study population. Diabetes was among 23.5% of the respondents and 11% of patients had h/o smoking.[25] Co-morbid conditions can make this condition even more troublesome to treat. Early diagnosis, thorough investigations, and early management can help in better outcomes of the patients.

In this current study, for 50% of the respondent's right lung involvement occurred, for 33% of cases left lung involvement occurred whereas for 17% of the patient's bilateral lung involvement happened.

In this study, for 56.7% of the cases, the empyema thoracis was due to tubercular causes. Among the patients with tubercular empyema, 10.0% were sputum positive, 10.0% were plural fluid positive, 13.3% clinico-radiologically positive, 10.0% were both sputum and pleural fluid positive and 13.3% were positive on culture. A similar study in India found that regarding the diagnosis of tubercular empyema, pleural fluid smear for AFB was positive in 21.5% of the patients, sputum smear was positive for 26% of cases which was almost similar to our study.[25]

Among the non-tubercular empyema, S. aureus was among 6.7% cases, S. pyogens were among 13.3% cases, gram-negative bacilli were among 6.7% cases, polymicrobial was found among 3.3% cases and 16.7% cases were sterile. This finding was almost similar to some other Indian studies.[22,25]

Ciprofloxacin was sensitive to 13.3% gram (+)ve and 33.3% gram (-)ve organism whereas it was resistant to 6.7% gm(+)ve and 46.7% gm (-)ve organisms. Gentamicin was sensitive to 33.3% gm (+)ve and 26.7% gm (-)ve organisms whereas resistant to 40.0% gm (-)ve organisms. Ceftazidime was sensitive to 33.3% gm (+)ve and 30.0% gm (-)ve organisms whereas resistant to 36.7% gm (-)ve organisms. Amikacin was sensitive to 26.5% gm (+)ve and 16.7% gram (-)ve organisms whereas resistant to 56.7%

gram (-)ve organisms. Aztreonam was sensitive to 33.3% gm (+)ve and 36.7% gram (-)ve organisms whereas resistant to 30.0% gram (-)ve organisms. Meropenem was sensitive to 20.0% gm (+)ve and 56.7% gram (-)ve organisms whereas resistant to 23.3% gram (-)ve organisms. Netilmicin was sensitive to 16.7% gm (+)ve and 56.7% gram (-)ve organisms whereas resistant to 26.7% gram (-)ve organisms. Cefepime was sensitive to 26.7% gm (+)ve and 46.7% gram (-)ve organisms whereas resistant to 26.7% gram (-)ve organisms. Colistin sulfate was sensitive to 26.7% gm (+)ve and 73.3% gram (-)ve organisms. Tazobactam+Piperacillin was sensitive to 16.7% gm (+)ve and 20.0% gram (-)ve organisms whereas resistant to 3.3% gram(+)ve and 20.0% gram (-)ve organisms. In this present study, among the isolated gram (+)ve organisms, S. Aureus showed highest sensitivity to Gentamicin, Ceftazidime, Amikacin, Aztreonam, Meropenem, Netelmicin, Cefepime and Colistin sulphate, s. Pyogens showed highest level of sensitivity to Gentamicin, Ceftazidime, Amikacin, Aztreonam, Meropenem, Netelmicin, Cefepime, Colistin sulphate and Tazobactam+Piperacillin. Besides, among the isolated gram (-)ve organisms, E.Coli showed highest level of sensitivity to Colistin sulphate (100%) followed by decreasing order Tazobactam+Piperacillin (75%), Ceftazidime (66.67%) and Meropenem (62.5%), Klebsiella showed highest level of sensitivity to Colistin sulphate (100%) followed by decreasing order Meropenem (80%) and Netelmicin (77.78%), Pseudomonas showed highest level of sensitivity to Colistin sulphate (100%) followed by decreasing order Tazobactam+Piperacillin (80%) and Netelmicin (77.78%). MTB showed highest level of sensitivity (100%) to all the antibiotics.

Empyema thoracis is difficult to manage but still presents as a challenge at referral tertiary care hospitals. Besides, co-morbid factors such as diabetes and immunosuppressive retroviral diseases may be implicated as the etiological reason for the resurgence of empyema in the present era of new and effective antibiotics. A high index of suspicion with careful monitoring and pleural fluid aspiration of non-responding parapneumonic effusions cases helps to identify cases of pyothorax at the earliest possible time. Culture sensitivity-based antibiotics and repeat culture tests will offer the best antibiotic choice.

CONCLUSION

In this study, in more than half of the patients with empyema thoracis, *mycobacterium tuberculosis* was observed as causative agent. Among the rest, gram positive organism, gram negative organism and polymicrobial organism were observed in a similar frequency. However, further multicentered study should be conducted with a larger sample size to delineate the bacteriological pattern of empyema thoracis in Bangladesh.

Limitations:

Statistically calculated sample size was not obtained that was relatively larger in relation to huge number of population. Post-surgical and post-traumatic empyema thoracis patients were not included in the study. Only one centre (SSMC and Mitford Hospital) patients were enrolled in this study.

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Declaration of Interest: The authors report no conflict of interest.

Ethical Consideration:

Ethical clearance was obtained from ethical review board of SSMC and Mitford Hospital. The objectives of this study along with risks and benefit were fully explained to the subjects in easily understandable local language and then informed written consent was taken from each patient. It was assured that all information and records would be kept confidential and the procedure would be helpful for both the physician and the patient in making rational approach of the case management.

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Original Article

Clinical Profile and Non-invasive Predictors of Fibrosis in a Newly Diagnosed Non-Alcoholic Fatty Liver Disease Patient in a Tertiary Health Care Center of Nepal

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) represents a spectrum of histopathologic abnormalities ranging from simple steatosis to the more aggressive non-alcoholic steatohepatitis, characterized by steatosis, parenchymal inflammation, hepatocellular ballooning and other evidence of hepatic injury. The objective of this study is to evaluate the demographic and anthropometric profile of non-alcoholic fatty liver disease and non-invasive predictors of fibrosis. This is a hospital-based observational study. A total of 280 patients were included in this study from the Department of Gastroenterology, Tribhuvan University Teaching Hospital from January 2019 to August 2021 were included. Patients presenting with non-alcoholic fatty liver disease were mostly (29.64%) of 36-45 age group. Two-third of the patients (66.78%) were asymptomatic. The mean body mass index of patients was 28.10±4.10 kg/m^2 and most of them (81.07%) had body mass index >25 kg/m^2. More than one third of the patients (40%) with non-alcoholic fatty liver disease had presence of metabolic syndrome. The mean (±SD) ultrasound attenuation parameter was 284.22±31.58 dB/m. Fatty liver index showed a positive and a medium strength correlation with fatty liver. On Spearman rank correlation, ultrasound attenuation parameter steatosis grading was correlated positively and strongly with the USG grading of fatty liver (p<0.001). On Pearson correlation, APRI, NFS and FIB-4 were positive but weakly correlated with liver stiffness measurement by FibroTouch but still the correlation was statistically significant (p<0.01). Fatty liver index has shown a good correlation with the presence of steatosis by a FibroTouch. Similarly, APRI showed the highest correlation in predicting liver stiffness in the population of Nepal. Other multicenter large scale prospective analytical studies would be required for further clarify of the results of such a kind of research.

Keywords: *Fatty liver index, fibro touch, non-alcoholic fatty liver disease, ultrasound attenuation parameter.*

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INTRODUCTION

Non-alcoholic fatty liver disease is a common entity which a clinician come across multiple times in their clinical practice. With the rising trend of sedentary lifestyle and unhealthy diet, obesity is in the rise, therefore the incidence of DM has increased since last few decades due to various reasons. All these socio-epidemiological changes have caused the incidence of NAFLD to increase. Globally, NAFLD is gradually overtaking alcoholic liver disease and viral hepatitis as the most common etiology of chronic liver disease. Thus, it has become imperative to define NAFLD/steatosis and the presence of fibrosis in the liver which is the primary driver of progression of liver disease. With the advancement of technology, developed nations have been shifting from the invasive liver biopsy in detecting liver fibrosis and steatosis to detecting liver stiffness by transient elastography. The high cost of this instrument has

precluded the clinician from a developing country like Nepal in having such instruments in their clinic.

Fatty liver is defined as accumulation of lipids within hepatocytes.[1] Fatty liver is a benign and reversible condition and depicts a non-specific response of liver to metabolic stress.[2] In 1980, Ludwig et al described the term non-alcoholic steatohepatitis (NASH) as a form of liver injury that was histologically consistent with alcoholic hepatitis but occurred in obese, diabetic females and who denied alcohol use.[3] The principle concept of the term non-alcoholic fatty liver (NAFL) denotes absence of other causes of fatty liver.[4] Although the diagnosis of NAFL can be made through imaging studies but to diagnose NASH, it requires histology.[5]

Incidence and prevalence of NAFLD is increasing over time mainly due to inappropriate food habit, weight gain, and sedentary lifestyle. Zobair et al. in 2019 showed that the global prevalence of NAFLD in general population is 25% whereas the global prevalence of NASH is 3% to 5%.[6] Accordingly, NASH is considered as the third commonest cause of liver disease after alcohol abuse and viral hepatitis.[7] The prevalence of NAFLD increases to 57.5% to 74% in obese persons and 90% in morbidly obese persons.[5] There is a strong association between occurrence of fatty liver and insulin resistance.[4]

The prevalence of NAFLD in Nepal is not known. Steatosis and fibrosis using vibration controlled transient elastography (VCTE) is done in a few selected centers in Nepal.[8] Thus, this study was intended to assess the clinical profile and non-invasive predictors of liver fibrosis using various scoring systems and transient elastography. This would validate these scoring systems in our population settings and thus could guide clinicians in centers where the more expensive transient elastography is not available.

MATERIALS AND METHODS

The study was carried out in the Department of Gastroenterology at Tribhuvan University, Institute of Medicine (TU, IOM), Maharajgunj, Kathmandu, Nepal for 1 year. This was a quantitative observational cross-sectional study. Non-probability consecutive sampling method was used in this study since all patients meeting the inclusion criteria were included in the study until the desired sample size was met. A sample size of 280 was estimated based on the sample size formula: $Z^2*P\ (1-P)/d^2$ where n = sample size, Z = Z statistics for level of significance, P = expected prevalence or proportion and d = precision. Sample size was calculated using a prevalence (P) of NAFLD of 24% with a 95% confidence interval (Z=1.96) and a precision(d) of 5%. The inclusion criteria were: patients with obesity, metabolic syndrome or diabetes, patients diagnosed with steatosis in USG incidentally, age > 16 years, those who provided informed consent. The exclusion criteria were: patients known to have significant alcohol history (>20 g/day in females and 30 g/day in males), taking drugs causing fatty liver and other hepatotoxic drugs, hepatitis B and C, autoimmune hepatitis (positive ANA), Wilson's disease, cardiac failure, pregnant woman, age < 16 years, those who did not provide informed consent.

Demographic variables like ethnicity, age, gender, diet, activity and clinical variables like chief complaints, significant examination findings, comorbid conditions if any were recorded. Laboratory variables like complete blood count, liver function test, fasting lipid profile, thyroid function tests, kidney function test, uric acid, viral markers, ANA and ferritin were assessed. USG was done by Philips iU22 USG machine. UAP was assessed by FibroTouch VCTE (Kerry Medical Limited). Various scores were calculated and correlated with the results of transient elastography.

RESULTS

A total of 280 patients with NAFLD were included; Here 112 (40%) patients with NAFLD had metabolic syndrome, while only 25 (8.92%) had syndrome Z. On reviewing the age, the mean age of patients was 44.94±11.99 years; 83, (29.64%) patients presenting with NAFLD were in age group of 36-45 years. Among the study population 164 (58.57%) were males as compared to females 116 (41.43%). Most of the patients were evaluated for NAFLD due to incidental detection of fatty liver in USG or asymptomatic elevation in transaminases done during routine investigation or done for evaluating other diseases.

Table 1 shows various anthropometric characteristics of the patients. The mean BMI was 28.10±4.16 (min: 19, max: 45) and 227 (81.07%) of the patients had BMI >25 kg/m^2. The mean waist circumference was 91.97±6.87 cm, whereas the mean for men and women were 91.05±4.83 cm and 93.97±8.83 cm respectively.

Table- I: Anthropometric Characteristics of Patients

Characteristics	Frequency (Percentage) /Mean ± SD (Min, Max)
Age (years)	44.94±11.99 (23, 82)
BMI (kg/m^2)	28.10±4.16 (19,45)
BMI >25 (kg/m^2)	227 (81.07%)
Waist circumference (cm)	
Male	91.05±4.83
Female	93.27±8.83
Total	91.97±6.87 (78, 122)
Hip circumference (cm)	
Male	96.47±5.88
Female	99.51±9.14
Total	97.73±7.56 (83, 132)
Mid-upper arm circumference (cm)	26.83±2.98 (22, 36)
Triceps skin fold thickness (mm)	15.58±3.62 (8,35)
Waist hip ratio	
Male	0.94±0.06
Female	0.93±0.02
Total	0.94±0.04

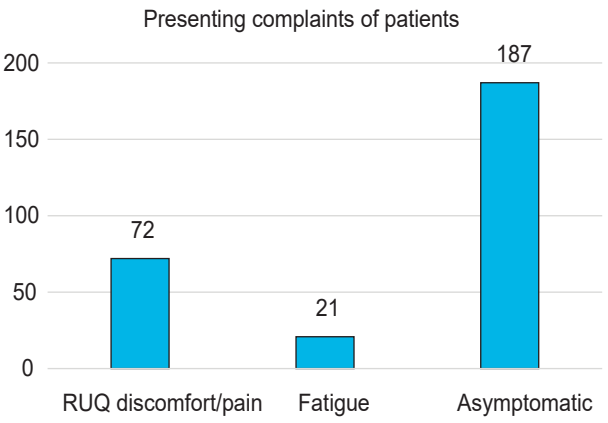

Figure- 1: Presenting Complaints of Patients

Figure 1 depict the presenting complaints of patients; here presenting complaint of right upper quadrant (RUQ) discomfort was 72 (25.71%) and fatigue was 21 (25%) among the symptomatic patients. Asymptomatic patients were 187 (66.79%).

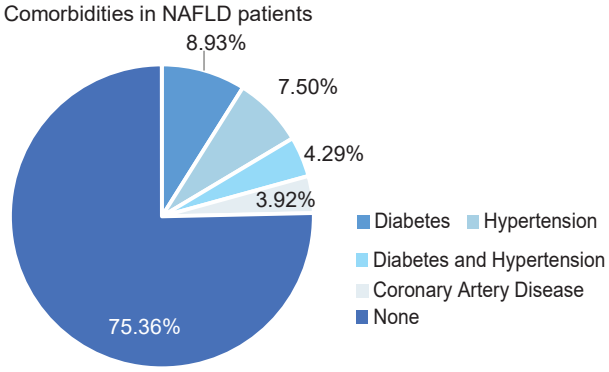

Figure- 2: Comorbidities in NAFLD Patients

Figure 2 states the distribution of comorbidities in NAFLD patients; here 75.36% had no comorbidities, where diabetes mellitus, hypertension, both diabetes and hypertension, coronary artery disease were found in 8.93%, 7.50%, 4.29% and 3.93% respectively.

Table II contains the distribution of baseline laboratory parameters of the patients. Here Mean±SD with range (minimum, maximum) of fasting lipid profile, liver function test, total protein, albumin, uric acid and fasting blood glucose were measured. The Mean±SD with range (minimum, maximum) were total cholesterol 4.10±2.87 mmol/L (2, 38), HDL 1.10±0.42 mmol/L (0.4, 4), LDL 2.27±0.90 mmol/L (0.5, 5), Triglyceride 2.68±2.11 mmol/L (0.8, 28), Total bilirubin 15.12±8.62 mmol/L (4, 66), Direct bilirubin 3.90±3.77 µmol/L (1, 47), AST 47.88±46.71 IU/L (10, 635), ALT 63.38±56.41 IU/L (10, 518), GGT 54.40±37.07 IU/L (10, 269), ALP 132.88±87.41 IU/L (38, 573), Total protein 73.31±6.43 gm/L (54, 91), Albumin 43.17±5.31 gm/L (22, 61), Uric acid 294.49±71.49 umol/L (150, 600) and Fasting blood glucose 5.33±1.78 mmol/L (3, 21).

Table- II: Baseline Laboratory Parameters of the Patients

Characteristics	Mean ± SD (Min, Max)
Total cholesterol (mmol/L)	4.10±2.87 (2, 38)
HDL cholesterol (mmol/L)	1.10±0.42 (0.4, 4)
LDL cholesterol (mmol/L)	2.27±0.90 (0.5, 5)
Triglyceride (mmol/L)	2.68±2.11 (0.8, 28)
Total bilirubin (µmol/L)	15.12±8.62 (4, 66)
Direct bilirubin (µmol/L)	3.90±3.77 (1, 47)
AST (IU/L)	47.88±46.71 (10, 635)
ALT (IU/L)	63.38±56.41 (10, 518)
GGT (IU/L)	54.40±37.07 (10, 269)
ALP (IU/L)	132.88±87.41 (38, 573)
Total protein (gm/L)	73.31±6.43 (54, 91)
Albumin (gm/L)	43.17±5.31 (22, 61)
Uric acid (umol/L)	294.49±71.49 (150, 600)
Fasting blood glucose (mmol/L)	5.33±1.78 (3, 21)

Table III refers to the ultrasonography grading of fatty liver and FibroTouch findings of the patients; the mean (±SD) UAP was 284.22±31.58 dB/m, but 7.1% of the patients diagnosed to have NAFLD by USG had no steatosis (S0) during UAP evaluation by FibroTouch. On Spearman rank correlation, UAP steatosis grading was correlated positively and strongly with the USG grading of fatty liver (spearman rank correlation 0.653, p<0.01).

Table-3: Ultrasonography grading of fatty liver and FibroTouch findings of the patients

Characteristics	Categories (Percentage)	Frequency
USG grading of fatty liver	1	96 (34.3%)
	2	116 (41.4%)
	3	68 (24.3%)
Steatosis grading by UAP	S0	20 (7.1%)
	S1	37 (13.2%)
	S2	108 (38.6%)
	S3	115 (41.1%)
UAP (Mean±SD {Min, Max})	284.22±31.58 (191, 400)	
Fibrosis grading by LSM	F0-F1	128 (45.7%)
	F2	81 (28.9%)
	F3	49 (17.5%)
	F4	22 (7.9%)
LSM (Mean±SD {Min, Max})	7.98±2.92 (3, 18)	

Table IV shows Pearson's correlation coefficient and the p-value for each of correlations which depict that weight and BMI are positively and largely correlated with UAP value and the correlation is statistically significant (p<0.01). Waist circumference was positively and had medium correlation with UAP value and the correlation is statistically significant (p<0.01). Metabolic syndrome and ALT are positively but small correlation with UAP value, but the correlation was statistically significant (p<0.01). Although, total cholesterol, LDL and fasting blood glucose had positive and small correlation with UAP but it was statistically insignificant.

Table 4. Correlation of UAP Values of FibroTouch with Other Covariates

Covariates	Pearson Correlation	P-value
Age	-0.072	0.23
Weight	0.51	<0.01
Waist circumference (cm)	0.413	<0.01
BMI	0.572	<0.01
Metabolic syndrome	0.231	<0.01
Total cholesterol (mmol/L)	0.105	0.078
HDL cholesterol (mmol/L)	-0.143	0.017
LDL cholesterol (mmol/L)	0.107	0.074
Triglyceride (mmol/L)	-0.004	0.948
ALT (IU/L)	0.219	<0.01
Fasting blood glucose (mmol/L)	0.038	0.522

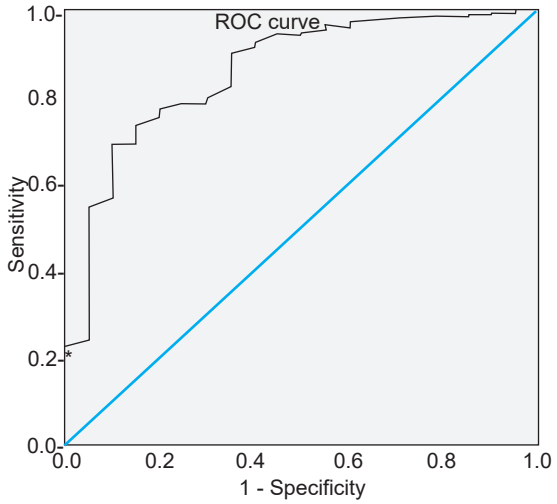

Figure- 3: ROC curve showing a significant area under curve (AUC) of FLI

Figure 3 demonstrates the Receiver Operating Characteristic (ROC) curve; here, ROC curve shows a significant area under curve (AUC) of 0.859. Fatty liver index (FLI) showed a positive but a medium strength correlation with fatty liver as shown by FibroTouch (correlation coefficient value 0.381, p-value <0.01).

Table 5 describes the correlation of non-invasive predictors of fibrosis and stiffness shown by FibroTouch; on pearson correlation, APRI, NFS and FIB-4 were positively but weakly correlated with LSM by FibroTouch but still the

correlation was statistically significant (p<0.01). BARD was positively correlated but it was statistically insignificant.

Table- 5: Correlation of non-invasive predictors of fibrosis and stiffness shown by FibroTouch

Covariates	Pearson Correlation	AUC	P-value
APRI	0.194	0.594	<0.01
NFS	0.212	0.536	<0.01
FIB-4	0.267	0.578	<0.01
BARD	0.009	0.490	0.883
Metabolic syndrome	-0.02		0.739

DISCUSSION

Nonalcoholic fatty liver disease represents a major public health concern. It is associated with type 2 diabetes, metabolic syndrome, and other cardiovascular risk factors, and may lead to fibrosis, cirrhosis, liver cancer, liver failure requiring liver transplant, and mortality. A total of two hundred eighty patients with NAFLD were included in the study. On reviewing the age, patients presenting with NAFLD were mostly of 36-45 age group (N=83, 29.64%). The mean age was 44.94±11.99 (min: 23, max: 82).

Most of the study population were males (N=164, 58.57%) as compared to females (N=116, 41.43%). This pattern of distribution of NAFLD in females is believed to be due to alteration in sex hormone levels, specifically reduced estrogens and increased androgens during and after menopause. Most of the patients were evaluated for NAFLD due to incidental detection of fatty liver in USG or asymptomatic elevation in transaminases done during routine investigation or done for evaluating other diseases which was similar to the findings shown by Joel Z. Stengel et al.[9] Right upper quadrant (RUQ) discomfort was the most common presenting complaint among the symptomatic patients which was on accordance with study done by Metin Basaranoglu et al.[10] Most of the patients did not have any comorbidities. Diabetes mellitus was the most common comorbidity present in these patients. More than one third of the patients with NAFLD had presence of metabolic syndrome (N=112, 40%). Similar finding was shown by Raxit Kumar Jinjuvadia et al. in a study evaluating 11,674 United States population. The mean BMI was 28.10±4.16 (min: 19, max: 45) which was similar to the study done by Sadroddin Lahsaee et al.[11] 227 (81.07%) of the patients had BMI >25 kg/m^2 which implied that more than three forth of patients with NAFLD were obese. 9.29% of patients had lean NAFLD. The mean waist circumference was 91.97±6.87 cm, whereas the mean for men and women were 91.05±4.83 cm and 93.97±8.83 cm respectively which shows that majority of patients had waist circumference higher than the cutoff indicated for Asian population by International Diabetes Federation.

This study showed fatty liver index (FLI) had a positive but a medium strength correlation with fatty liver as shown by FibroTouch (correlation coefficient value 0.381, p-value <0.01). This depicted a good strength in predicting the presence of fatty liver without using FibroTouch which could be of great benefit in a resource limited country like ours. Receiver operating characteristic (ROC) curve shows a significant area under curve (AUC) of 0.859.

Since the transient elastography instrument is costly, it is not available widely in a resource limited country like Nepal. In addition, liver biopsy for evaluating the presence of liver fibrosis is not practical in all patients. Thus, non-invasive predictors for detecting and grading liver fibrosis is of paramount importance. Various non-invasive predictors have been developed. This study highlights the correlation of these predictors with LSM value given by elastography. On Pearson correlation, APRI, NFS and FIB-4 were positively but weakly correlated with LSM by FibroTouch but still the correlation was statistically significant (p<0.01) in this study. Whereas, BARD was positively correlated but it was statistically insignificant (p=0.883). Area under the ROC curve (AUROCs) of APRI, NFS, FIB-4 and BARD score were 0.594, 0.536, 0.578 and 0.490 respectively. Despite these predictors having positive correlation, APRI, NFS and FIB-4 had weak correlation and BARD had statistically insignificant correlation.

In a study done by Alhankawi, Dhuha et al. FIB-4 and APRI correlated significantly with fibroscan score (r=0.472, p<0.0001 and r=0.418, p<0.0001).[12] The aforementioned study also showed an AUROCs of FIB-4 and APRI were 0.705 and 0.644 respectively.[12] Similarly, study done by Sebastian Zenovia et al. revealed a significant correlation between LSM values and APRI (r = 0.19, p = 0.020), FIB-4 index (r = 0.34, p < 0.001), and NFS (r = 0.30 p < 0.001).[13] Study done by Savvoula Savvidou et al. in Greek Tertiary Liver Centers showed a positive correlation of BARD score with LSM with

AUROC of 0.724±0.041 (95% CI 0.645-0.804), p<0.001.[14] Our study revealed that APRI had a higher accuracy for the prediction of significant fibrosis followed by FIB-4 and NFS. BARD score had the least accuracy in predicting fibrosis.

CONCLUSION

The role of non-invasive predictors arises which predict the presence of steatosis and fibrosis by using various biomarkers. Although, these non-invasive predictors have been tested in other countries, they have not been studied in the population of Nepal. Thus, the aim of this study was to evaluate the accuracy of these non-invasive predictors and its correlation with FibroTouch. Fatty liver index has shown a good correlation with the presence of steatosis by a FibroTouch. Similarly, APRI has shown the highest correlation in predicting liver stiffness in the population of Nepal. A good correlation was also seen with FIB-4 and NFS but BARD score showed the least accuracy. Other multicenter large prospective studies are required to further clarify the results of such a kind of research.

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Original Article

Assessment of Post-Operative Complications after Radial Recurrent Artery Flap for Management of Wound Coverage in and Around the Elbow Region

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Abstract

Complex elbow wound management is a common issue of reconstructive surgery which deals with burns (electric and flame burn), road traffic accidents (RTA), machineries and industrial accidents, tumor excision, the release of post-burn scar contracture, complications related to orthopedic reconstruction etc. A stable soft tissue cover is required for reconstructive purposes for such wounds management. In this ground surgeons apply suitable procedure and consider wound aetiologies to meet better outcome. Surgeons also permit the early elbow mobilization to preserve a range of motion after complex elbow wound management. Radial recurrent artery flap, in particular, provides durable coverage for medium-sized elbow defects as well as an early range of motion of the elbow joint. Some complications like marginal and partial flap necrosis are observed in some of the cases. The aim of the study was to assess the clinical outcome and complications after radial recurrent artery flap for the management of wound coverage in and around the elbow region. This is a prospective type of observational study conducted in the Department of Plastic Surgery, Dhaka Medical College and Hospital (DMCH), Dhaka. There were selected 20 patients according to inclusion and exclusion criteria over 17 months from October 2016 to February 2018. The patients were kept under follow-up of at least 2 months postoperatively. Findings of observation were recorded in a preformed data collection sheet and all data were compiled in a master table. Statistical analysis of the results was obtained by using statistical package for social science (SPSS), version- 17. In this study, the mean age of the patients was 25.4 years. The age range was 05 years to 50 years. Maximum patients (40%) were in age group 16 to 25 years. Among the injured patients, male – female ratio was 4:1. More than half of the injuries (55%) were caused by electric burn; other injuries were trauma (15%), flame burn (10%), contact burn (05%), and 15% by different causes. Radial recurrent artery flap was used to cover the cubital fossa in 13 patients (65%), the posterior aspect of the elbow in 5 patients (25%) and amputation stump in 02 patients (10%). The cubital fossa was the most used site in 15 patients. Here, the mean dimension of the wound was 80.28 cm^2 and the mean dimension of the flap was 70.43cm^2. Among 20 patients, 16(80%) patients showed no complication, marginal flap loss in one patient, partial flap necrosis in two patients, and total flap loss in one patient were observed. No history of graft loss and the donor site of the skin graft healed well. One case showed marginal flap loss, which is managed conservatively and healed by secondary intention. Two cases showed partial flap loss and another case showed total flap loss which is managed by excision of non-viable part followed by STSG. In 17 (85%) cases donor sites of flaps are closed primarily. One patient (05%) needed primary closure and STSG. Two patients (10%) needed STSG to cover the donor site. In most of the cases, about 80% showed excellent outcomes. Good outcomes in three cases (distal marginal and partial flap loss) and poor outcomes in one case (total flap loss) were observed. This study showed that Radial Recurrent Artery Flap is a good option for coverage of soft tissue defects in and around the elbow joint. It is a single-stage procedure allowing early mobilization and thereby preventing stiffness of the elbow joint. It also showed the rise of some complications that might be uncomfortable for patients.

Keywords: *Radial recurrent artery flap, elbow joint, STSG (split thickness skin graft).*

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INTRODUCTION

Open soft tissue abnormalities around the elbow joint are frequently observed as a result of burns, trauma, internal fixation of complex fractures, and the relaxation of post-burn contractures. Stable coverage is necessary because these conditions often expose functionally significant tissues such as blood vessels, nerves, bones, and tendons. Although both local and free flaps can be used to address these problems, local flaps are typically preferred over muscle flaps with skin grafts. Local flaps require less operative time and provide a more aesthetically pleasing tissue match in terms of both color and texture. However, there are few local axial flaps suitable for use in the elbow joint, making these abnormalities particularly challenging to reconstruct. For anterior and posterior elbow lesions, the radial recurrent artery (RRA) flap offers a flexible and reliable option. The primary benefits of this flap include its consistent axial pedicle, simplicity of dissection, favorable aesthetic outcomes, and the ability to perform a quick, one-stage operation that avoids long-term immobilization of the affected elbow joint. Importantly, this procedure does not involve the sacrifice of a major artery or nearby muscle.[1] The radial artery (64%), the area just below the elbow joint, or the distal portion of the brachial artery (18%) are the most common sources of the RRA.[2] It supplies the extensor carpi radialis longus, extensor carpi radialis brevis, and the elbow joint as it ascends between the branches of the radial nerve, lying first on the supinator and then between the brachioradialis and brachialis, anastomosing with the RCA. Additionally, it provides skin coverage over a portion of the arm's lateral surface.[3] At the cubital fossa, the radial nerve splits into deep and superficial branches. The radial portion of the dorsal hand is innervated by the superficial branch of the radial nerve (SBRN), which is a sensory nerve.[4] One significant effect this anomaly may have on the radial free forearm flap (RF) is that it may cause the RA to flow more superficially in the forearm, making it susceptible to injury through the proximal skin cut.[5] Malperfusion may occur in the proximal skin paddles, and it is not always possible to rework the skin paddle in the middle of the casing. When designing a flap paddle, the surgeon should first establish the anatomy of the RA through proximal pedicle exploration if a proximal skin paddle is required.[6] However, the RF flap donor site has several drawbacks, including loss of skin graft, impaired motor function, and sensory disruption. Specifically, sensory disruption can lower patients' quality of life after surgery. Patients frequently report paresthesia and/or discomfort following damage to the SBRN during RF flap harvest. These symptoms seldom interfere with daily activities and are often temporary unless the SBRN is completely removed. However, some patients experience chronic neuropathic pain that lasts a lifetime. Additionally, patients with paresthesia who are young and active have a significant chance of suffering another injury. Due to diminished sensibility, there is a risk of contact burn on the dorsal hand.[4] Therefore, it is critical to minimize sensory disruption during RF flap harvest.

METHODS

This was a prospective type of observational study done in the Department of Plastic Surgery, Dhaka Medical College and Hospital, Dhaka. Patients were selected according to inclusion and exclusion criteria over 17 months from 1st October 2016 to February 2018 where the sample size was 20. Wounds in and around the elbow resulting from a burn, tumor excision, trauma, post-burn contracture release, etc. necessary for flap coverage were among the inclusion criteria. Patients with potential injuries to the pedicle of the donor site due to previous trauma or surgery, and patients with significant co-morbid conditions either with psychiatric disorders or with polytrauma and other life-threatening injuries were excluded from the study. The patients were kept under follow-up of at least 2 months postoperatively. Findings of observation were recorded in a preformed data collection sheet and all data were compiled in a master table first. Statistical analysis of the results was obtained by using a statistical formula and calculator. Statistical analysis of the result obtained by using Windows-based computer software devised with Statistical Package for Social Science (SPSS-17).

RESULTS

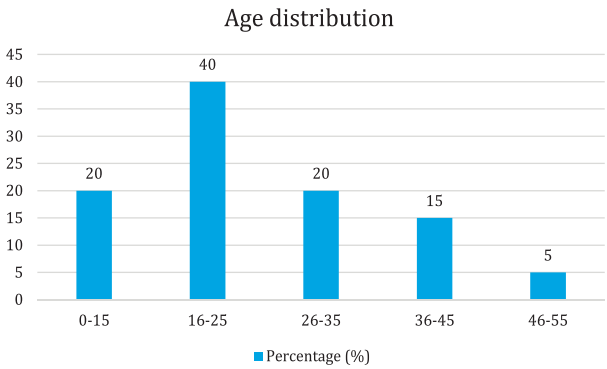

Figure- 1: Age distribution of the participants (N=20)

Figure 1 illustrate the age distribution of the participants; among them the mean age was 25.4 years. Here, 40% was within the age group of 16-25 years, while 20% was under 16 years of age and another 20% was in age group of 26-35 years.

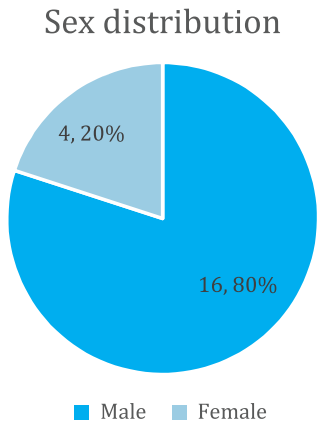

Figure- 2: Gender distribution of the participants (N=20)

Figure 2 represents the distribution of sex of the participants, where 80% of the participants were male and rest of them were female.

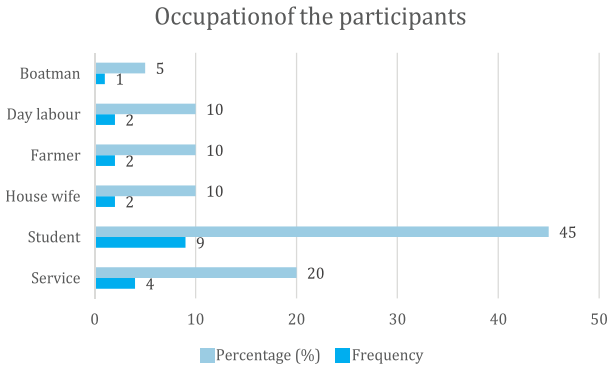

Figure- 3: Distribution of the participants by occupation (N=20)

Figure 3 state the distribution of the participants by occupation; 45% of the participants was students, where 20% was service holder. Day laborer, farmer, and housewife each of them held 10% of the study population.

Table I shows the distribution of patients by cause of injuries; here, 55% of the injuries happened due to electric burns. Other injuries caused by trauma 15%, flame burn 10%, contact burn 05%, tight plaster 05%, the release of post-burn scar contracture 05% and excision of squamous cell carcinoma 05%.

Table- I: Distribution of patients by cause of injury (N= 20)

Cause of injury	Frequency	Percentage (%)
Electric burn	11	55
Trauma	3	15
Flame burn	2	10
Contact burn	1	5
Tight plaster	1	5
Release of post-burn scar contracture	1	5
Excision of squamous cell carcinoma	1	5

Table II contains the sites of wound, dimension of wounds and also dimension of flaps. Here 65%, 25% and 10% wounds were in the site of cubital fossa, posterior aspect of elbow and amputation stump respectively. In mean dimension of wounds was 80.8 cm^2, where length was 11.28 cm and width was 7 cm. The mean dimension of flaps was70.43cm^2 where length was 13.3 cm and width was 5.28 cm.

Table- II: Site of wounds, dimension of wounds and flaps (N=20)

Variables	Number of Patients	Percentage
Site of wound		
Cubital fossa	13	65%
Posterior aspect of elbow	5	25%
Amputation stump	2	10%
Mean dimension of wounds	**Measurement**	
Length	11.28 cm	
Width	7 cm	
Wound	80.8 cm^2	
Mean dimension of flaps	**Measurement**	
Length	13.3 cm	
Width	5.28 cm	
Flap	70.43 cm^2	

Table- III shows distribution of patient by postoperative complication, where 10% of complications were found to be partial flap necrosis; each of the marginal and total flap necrosis was found in 05% of patients.

There was no history of graft loss. Donor sites of flaps and skin grafts healed well and 80% of patients showed no complications.

Table-III: Distribution of patient by postoperative complication (N=20)

Complication	Frequency	Percentage
Marginal flap necrosis	1	5 (%)
Partial flap necrosis	2	10 (%)
Total flap necrosis	1	5 (%)

Table IV states the management of complications 01 case showed marginal flap loss which is managed conservatively and healed by secondary intention. 02 cases showed partial flap loss and another case showed total flap loss which is managed by excision of non-viable part followed by STSG.

Table-IV: Management of complications (N=20)

Complication	Management	Frequency	Percentage
Marginal flap loss	Excision & secondary healing	1	5
Partial flap loss	Excision and STSG	2	10
Total flap loss	Excision and alternate method of reconstruction	1	5

In Table V contains the distribution of patients by mode of donor site closure 17 (85%) cases of donor sites of flaps are closed primarily, 01 patient (05%) was needed primary closure and STSG and 02 patients (10%) were needed STSG to cover the donor site.

Table- V: Distribution of patients by mode of donor site closure (N=20)

Closure	Frequency	Percentage (%)
Primary closure	17	85
Primary closure +STSG	1	5
STSG alone	2	10

Table VI represents the distribution of results by reconstruction; here 16(80%) cases showed excellent outcomes, good outcomes in 03 cases (distal marginal and partial flap loss) and poor outcomes in 01(5%) case (total flap loss).

Table-VI: Distribution of results by reconstruction (N=20)

Outcome	Criteria	Percentage (%)
Excellent	Excellent flap adhesion, no infection, no flap loss	80
Good	Distal marginal flap loss, partial flap loss, hypertrophic scar over donor site	15
Poor	Complete flap loss requiring alternate procedure, wound dehiscence over donor site and subsequent ugly scar	5

DISCUSSION

In this study, the mean age of the patients was 25.4 years, with an age range from 5 to 50 years, where the majority of cases were between 16 to 25 years of age. Similarly, Ashfaq F. et al. used a reverse lateral arm flap with an age range from 13 to 30 years and a mean age of 23.8 years.[7] A study by Khaled M.S. et al. also illustrated reverse lateral arm flaps for elbow coverage with an age range from 7 to 50 years, closely aligning with our study. When considering gender, male predominance was observed in our study, with 80% of the 20 patients being male and 20% female. Similarly, Khaled M.S. et al. showed 54% male prevalence in their study, where out of 30 cases, only 46% were female.[8] The etiology of soft tissue defects in this study included electric burns, trauma, flame burns, and others. Among these, electric burns and trauma were the primary reasons for reconstruction, accounting for 55% and 15% of cases, respectively. The etiology in the study by Tiernan E., Healy C., et al. included trauma, cutaneous malignancy excision, and radial forearm free flap donor defects, while Khaled M.S. et al. used distally based lateral arm flaps to cover elbow defects caused by electric burns, trauma, release of post-burn scar contracture, and other reasons.[8, 9] This study used the flap to cover the cubital fossa in 13 cases, the posterior aspect of the elbow in 5 cases, and the amputation stump in 2 cases. Similarly, the study by Tung TC et al. used this flap in 7 patients for the reconstruction of posterior soft tissue defects of the elbow, and another

study by Culbertson JH et al. used this flap to cover the cubital fossa in a patient.[10, 11] Here, the study shows that the cubital fossa was the most frequently used site in 13 patients. The wound length averaged 11.28 cm and the width 7 cm, with a mean wound dimension of 80.8 cm^2. The flap length averaged 13.3 cm, the width 5.28 cm, and the mean flap dimension 70.43 cm^2. Prant IL. et al. used this flap for wound sizes of 4 to 10 cm and an average wound area of 30 to 80 cm^2, closely matching our findings.[12] Among the 20 cases in our study, no complications were observed in 16 cases. Marginal flap loss occurred in one case, partial flap loss in two cases, and total flap loss in one case, which were managed by excision of the non-viable part followed by split-thickness skin grafting (STSG). Similarly, Khaled MS et al. showed that out of 30 cases, there was marginal flap loss in 3 cases, significant flap loss in 2 cases, complete flap loss in 2 cases, and no loss in 23 cases.[8] In 17 patients (85%), the donor site was primarily closed. Two patients required STSG to cover the donor site, and one patient required primary closure and STSG. There was no discernible donor site morbidity, such as unstable scars, hypoesthesia, or hypertrophic scars. Khaled MS et al. noted donor site morbidity such as stretched scars, hypertrophic scars, and hypoesthesia in a few of his cases.[8] In our study, 16 cases showed excellent outcomes, three cases (with distal marginal and partial flap loss) showed good outcomes, and one case showed poor outcomes (total flap loss). Lai CS et al. reported uneventful postoperative outcomes, satisfactory cosmetic results at both donor and recipient sites, and normal elbow function in their study.[12]

Limitations of the Study

The maximum dimension of the flap was not adequately assessed. The increased range of motion of the elbow joint due to the operation or physiotherapy was also not distinguished. The study was conducted in a single hospital with a small sample size, which may not fully represent the actual results.

CONCLUSION

The radial recurrent artery flap proved to be dependable and durable, with no donor site morbidity. This is a good substitute when reconstructing a small to moderate-sized elbow defect that requires a thin, flexible flap. The range of motion of the elbow joint is guaranteed and influenced by early postoperative exercise. Some limitations (small flap size, limited vascular caliber) are still there to solve and some complications such as loss of skin graft, impaired motor function, and sensory disruption, chronic neuropathic pain may be observed in some of the cases while managing wound coverage in and around the elbow region. Apart from that, it's a useful option for addressing defects in the elbow region.

Ethical approval: The study was approved by the Institutional Ethics Committee. Confidentiality was maintained. Permission was taken from the department and institution to perform the study.

RECOMMENDATION

The findings of this study may be a demonstration of radial recurrent artery flap for management of wound coverage in and around the elbow region. The findings of this study will guide the surgeons for more accurate assessment of the outcome. Larger sample size and multi-centered data with sufficient period time are required for further study and better outcome.

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Case Report

Systemic Lupus Erythematosus Complicated by Portal Vein Thrombosis: A Case Report

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Abstract:

A 24-year-old female got admitted in a remote hospital with one and half month previous history of gradually increasing swelling of the abdomen followed by swelling of the both legs and face without any discernable etiology. Later she is diagnosed as a case systemic lupus erythematosus (SLE) based on clinical features and serology. She had neither any history of having pro-thrombotic risk factor nor any history of deep vein thrombosis. Her Anti-β2 Glycoprotein 1 (Ab IgM & IgG) was marginally positive. Her ultra-sonogram of abdomen showed moderate ascites, gross thrombosis & stenosis in portal system (main trunk of portal vein, both proximal branches of portal vein, splenic vein at pancreatic area, superior mesenteric vein *at confluence) that were 100% blocked that also supported by CT scan of abdomen and Doppler ultra-sonogram. Her Doppler ultra-sonogram of lower limbs were normal. She was treated initially with albumin infusion, enoxaparin, warfarin, aspirin, hydroxychloroquine and medium dose prednisolone.*

Keywords: *portal hypertension, systemic lupus erythematosus, anticardiolipin antibody*

INTRODUCTION

Thrombotic events are well-known complications of systemic lupus erythematosus (SLE) and have been largely related to the presence of the lupus anticoagulant.[1,2] Portal vein thrombosis (PVC) results from a combination of local and systemic prothrombotic factors. In acute portal vein thrombosis, patients may be asymptomatic or present with life-threatening intestinal ischemia and infarction. In the chronic stage, patients generally present with complications related to portal hypertension, such as variceal bleeding and hypersplenism.[3] However, no cause is identified in more than 25%of patients.[4] The case report will highlight the abdominal swelling as a remarkable symptom in portal vein thrombosis. The main objective to report the case is unusual thrombotic feature of SLE.

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*For correspondence

CASE REPORT

A 24-year-old female, homemaker from southwestern district of Bangladesh got admitted in a remote hospital with one and half month previous history of gradually increasing swelling of the abdomen followed by swelling of the both legs and face without any history of jaundice or melena, breathlessness, fever. She was treated then conservatively with diuretics without any diagnosis or any resolution of her ascites. Six months later, again, she had started to have abdominal and pedal swelling with a gradually increasing puffy face; then she had got herself admitted in the same hospital for her diagnosis. This time extensive investigations were carried out and found raised ESR (45 mm in 1st hour), homogenous pattern of ANA positivity (28.5 u/mL) (reference value: >10 U/ml) with raised Anti-ds DNA Anti-ds DNA – 18.7 (reference value: <20 IU/ml), low C3 (43) (reference value: 80-170 mg/dL) and C4 (19) (reference value: 20-50 mg/dL). Her Anti-β2 Glycoprotein 1 (Ab IgM & IgG) were marginally positive but Lupus anticoagulant and Anti-Cardiolipin (Ab IgM & IgG) were negative. The hepatitis viral markers were negative. Her serum albumin (2, 2.4 and 1.47 g/dL in three occasions reference value is 3.5–5.0 g/dL), D-dimer (2.62 mcg/mL reference value is <0.5), INR (1.0), aPTT (30 seconds reference value is 30-40 seconds), UTP (0.14 g/day reference value is <0.150 gm/d) were carried out. The ascitic fluid study showed protein (3.0 g/dL reference value is 2.5 grams/dL) and ADA (5.18 IU/L reference value is 36 to 40 IU/L). The upper GI endoscopy revealed congestive gastropathy with duodenal ulcer, her x-ray chest PA view was normal.

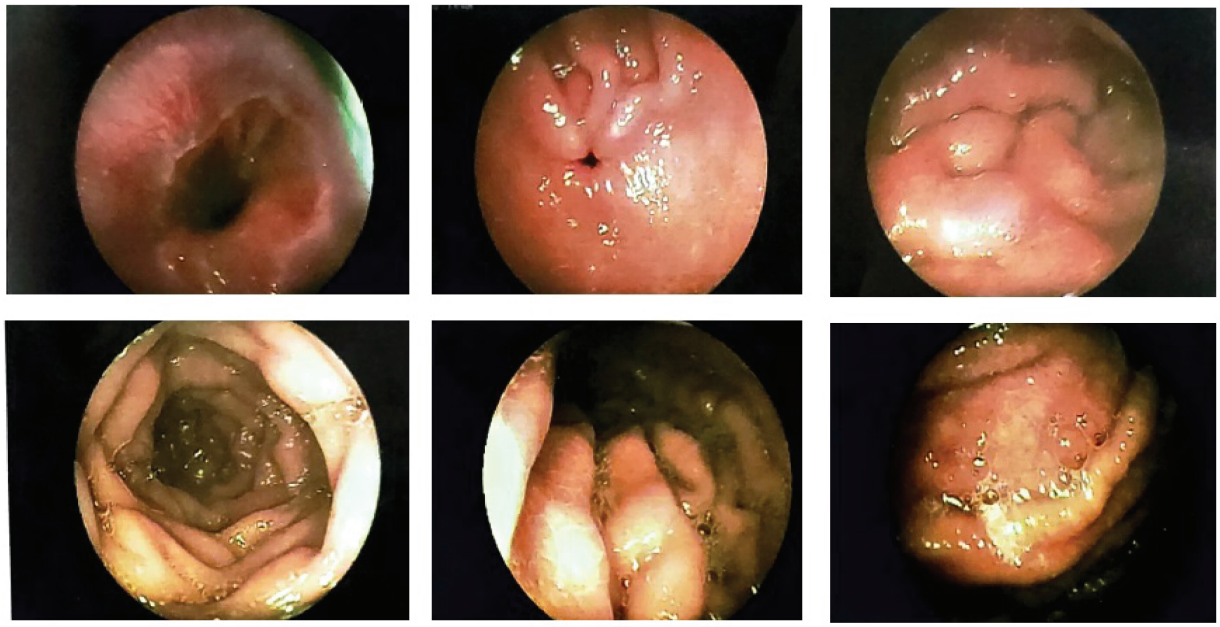

Figure 1 Upper GI endoscopy

At that time, ultra-sonogram of abdomen showed moderate ascites, gross thrombosis & stenosis in portal system (main trunk of portal vein, both proximal branches of portal vein, splenic vein at pancreatic area, superior mesenteric vein at confluence) which were 100% blocked. The upper GI endoscopy (Figure 1)

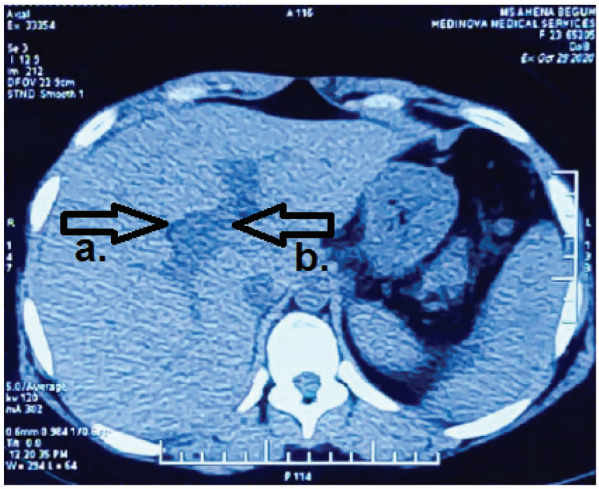

Figure 2 CT Abdomen

Upper GI endoscopy revealed congestive gastropathy as a normal esophagus without any varix where stomach revealed features of congestive gastropathy seen at the body and fundus and duodenum revealed multiple small superficial ulcer seen at the bulb, post-bulbar area and second part revealed portal hypertensive gastropathy. The CT scan of abdomen (**Figure 2**)

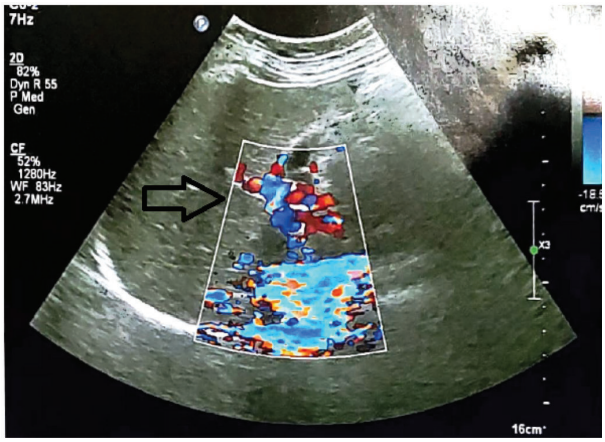

Figure 3 Doppler Ultrasound of portal and hepatic vein

Unenhanced axial CT scan of the abdomen showing an increase in the caliber of the portal vein (>13 mm) (a) that contains hyperdense material of portal vein thrombosis (b) revealed portal vein thrombosis with an enlarged portal vein. The Doppler ultra-sonogram of portal and hepatic vein revealed portal venous thrombosis with no flow with a peri-portal collateral circulation. (**Figure 3**)

The color Doppler ultrasound in a case of portal vein thrombosis, showing serpiginous vessels (arrow) in the periportal region.

Her Doppler ultra-sonogram of lower limbs were normal. She got symptomatic treatment without any improvement. Following primary management, she was referred to

tertiary hospital with new complaints of constant epigastric pain of recent onset with variable intensity that aggravates with food intake, associated with nausea and occasional vomiting. This time she also gave history of alopecia and photosensitivity. She was also suffering from constipation. She had received albumin infusion twice during her course of illness. She had neither any history of having pro-thrombotic risk factor nor any history of deep vein thrombosis. Her clinical examinations revealed she is overweight (BMI 27 kg/m2) with a puffy face. She was anemic, non-icteric, having bilateral pitting edema. Her abdominal examination revealed epigastric and bilateral hypochondriac tenderness without any organomegaly. Moderate ascites was present evidenced by shifting dullness. The bowel sound was audible. The examinations of all other systems including fundoscopy were unremarkable. During her hospital stay, she was initially treated with enoxaparin as 1 mg per kg/day, warfarin 5 mg/day, aspirin 75 mg/day, hydroxychloroquine 300 mg/day and medium dose prednisolone 0.5 mg/kg/day. After two weeks of the treatment her the patient symptomatically improved much. After readjustment of warfarin according to INR, the patient was discharged with a proper follow up schedule along with patient education about SLE and warfarin.

DISCUSSION

The PVT refers to the development of thrombosis within the extra-hepatic portal venous system draining into the liver.[5] It has been classified into 4 anatomic groups[6]:

(1) Thrombosis confined to the portal vein beyond the confluence of the splenic and superior mesenteric vein (SMV);

(2) Extension of thrombus into the SMV but with patent mesenteric vessels;

(3) Diffuse thrombosis of splanchnic venous system but with large collaterals;

(4) Extensive splanchnic venous thrombosis but with only fine collaterals.

The main mechanisms of PVT are due to disturbance of any element of the Virchow triad results in sluggish portal blood flow that occurs commonly in liver cirrhosis, hepatobiliary malignancies, gastric carcinoma, or extrinsic compression by lymph node or tumor.[7]

There are many medical conditions including Factor V Leiden deficiency, G20210A prothrombin gene mutation and surgical conditions can lead to thrombosis of the portal vein.[8, 9]

Table 1. Risk factors for portal vein thrombosis[10]

1. Acquired thrombophilia
   a. Antiphospholipid syndrome
   b. Paroxysmal nocturnal hemoglobinuria
2. Inherited thrombophilia
   a. Antithrombin deficiency
   b. Factor V Leiden
   c. Prothrombin gene G20210A mutation
   d. Protein C and S deficiency
3. Local factors
   a. Abdominal trauma
   b. Abdominal malignancy (eg, pancreatic cancer, hepatocellular carcinoma)
   c. Abdominal surgery (eg, splenectomy, liver transplantation)
   d. Endoscopic sclerotherapy
   e. Intra-abdominal inflammatory process (eg, cholecystitis, diverticulitis, pancreatitis)
   f. Transjugular intrahepatic portosystemic shunt
4. Systemic disorders
   a. Behçet syndrome
   b. Cirrhosis*
   c. Collagen vascular disease (eg, systemic lupus erythematosis)
   d. Inflammatory bowel disease
   e. Myeloproliferative syndrome (eg, polycythemia vera)

f. Pregnancy or exogenous hormone use

* Patients with decompensated cirrhosis are at higher risk for developing portal vein thrombosis than patients with compensated cirrhosis.

Our patient fulfilled the first classification. No definite time-frame found in the literatures to differentiate acute from chronic PVT, but studies of the chronic PVT considered in patients who developed symptoms <60 days prior to hospital assessment.[11]

Both acute and chronic PVT may be clinically asymptomatic and diagnosed incidentally during a radiologic examination for other reasons. The acute PVT patients may present with acute abdominal pain associated with or without fever. Our patient presented with epigastric pain that was not clinically specific for the portal

vein thrombosis. Sometimes, superior mesenteric vein thrombotic patients may have colicky abdominal pain and diarrhea. On the other hand, chronic PVT patients may present with symptoms related to complications of chronic PVT e.g. portal hypertension or portal cholangiopathy. The physical examination in most patients with acute PVT reveal no abnormalities though some patients with acute PVT may have an ileus and abdominal distension without other signs of intestinal obstruction.[12] Our patient presented with abdominal distention due to ascites. On the contrary, the patients with chronic PVT, even if asymptomatic, frequently have esophageal or gastric varices, and mostly of those present with gastrointestinal bleeding.[13-16]

Acute portal vein thrombosis (PVT) is diagnosed with abdominal imaging that demonstrates portal venous occlusion without the radiographic findings of chronic PVT. Radiographic findings in chronic PVT include demonstration of cavernous transformation of the portal vein and filling defects within the portal vein. A contrast-enhanced abdominal computed tomography (CT) scan can confirm the diagnosis, evaluate for predisposing conditions, assess the extent of the thrombosis, delineate the anatomical details, and detect evidence of intestinal infarction as well. Less suspicious patient can do a Doppler ultrasound. If the ultrasound is suggestive of acute PVT, an abdominal CT scan will be the next option for confirmatory diagnosis. Abdominal magnetic resonance imaging (MRI) is an alternative in patients who neither can undergo CT scan nor accept radiation exposure. Ultrasound with Doppler is an alternative; if CT and MRI are contraindicated or not available. Finally, a diagnosis of PVT is possible with portal venography; or by invasive procedure like superior mesenteric angiography that is generally not required.[17]

The primary management of acute portal vein thrombosis (PVT) is anticoagulation and when found; treatment of predisposing conditions. Anticoagulation is required to prevent extension of the clot and prevention of development of portal hypertension. The presence of predisposing conditions and the patient's comorbidities dictate the management of chronic portal vein thrombosis (PVT). Anticoagulant therapy should be initiated promptly in all patients, unless contraindicated because spontaneous restoration of patency is rare and recanalization of the portal vein prevents complication like portal hypertension that dictates the prognosis of the patient. Early anticoagulation results in better outcome e.g. chances of recanalization is 60% if therapy begins within the first week after symptom onset where only 20% if started within the first month. Anticoagulation needs to be continued indefinitely in patients with an underlying thrombophilic disorder. Therefore, our patient needs to be on life-long anticoagulation. Surgical thrombectomy is not recommended.[18] Predictors of survival have not been properly studied, the main determining factor appears to be advanced age and mesenteric venous thrombosis.[19]

For reduction of PVT-associated morbidity and mortality there are two broad objectives to be achieved, firstly, to reverse or prevent the advancement of thrombosis within the portal venous system; and secondly, to treat the complications of established PVT, most specifically gastrointestinal varices or biliary complications. (G. J. M. Webster et al.)

CONCLUSION

The PVT is a rare disease. A high index of suspicion needs to reach a clinical diagnosis of PVT considering the multiple risk factors, including inherited and acquired thrombophilic predispositions. Early diagnosis will certainly prevent both morbidity and mortality.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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Obituary news September 2023

BMA would like to express deep condolence on deaths of the following notable physicians in recent past:

Sl. No.	Name	Date of Death
1	Dr. Monjurul Hakim Tuhin	03/05/2023
2	Dr. Abur Rahman	05/05/2023
3	Dr. Md. Rafiqul Hossain Khokon	16/05/2023
4	Professor Dr. Shamsul Alam	16/05/2023
5	Dr. Md. Abdul Hamid Sarkar	18/05/2023
6	Dr. Abdul Mabud	24/05/2023
7	Professor Dr. Fakhrul Islam	27/05/2023
8	Dr. Faria Noor Anannya	30/05/2023
9	Dr. Eftekharul Alam Linkon	02/06/2023
10	Dr. Sajedur Reja Faruquee	04/06/2023
11	Dr. Mahfuja Chowdhury (Canada Emigrant)	13/06/2023
12	Dr. M. Arifur Rahman	22/06/2023
13	Dr. Avijit Kumar Singha	07/07/2023
14	Dr. Mahfuza Begum	07/07/2023
15	Professor Dr. M A Taher Khan	16/07/2023
16	Dr. Fatema Tuj Johora Rawnaq	22/07/2023
17	Dr. Abu Rafael Mohammad Rafi	26/07/2023
18	Dr. Hellol Dey	03/08/2023
19	Dr. Abdur Rahman	04/08/2023
20	Dr. Almina Deowan Mishu	07/08/2023
21	Dr. Sharifa Binte Aziz	11/08/2023
22	Dr. Kamrul Islam Jewell	12/08/2023
23	Professor Dr. Mozammel Haque	13/08/2023
24	Dr. Md. Abdul Kader Khan	30/08/2023
25	Dr. Sujauddula Rubel	02/09/2023
26	Professor Dr. Aynal Haque	04/09/2023
27	Professor Dr. Shakilur Rahman Roky	06/09/2023
28	Professor Dr. Rafiuddin Ahmed	13/09/2023
29	Professor Dr. S. A. Abdul Bari	14/09/2023
30	Dr. A. A. Mazharul Haque (Bengali Language Warrior)	22/09/2023
31	Professor Dr. Zinat Meraj Swapna	23/09/2023
32	Professor Dr. Delwar Hossain	29/09/2023

May Allah bless the departed souls.

Our heartiest commiseration to the deceased's family, our prayers are with them during this difficult moment of their life.

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