Clinical Features and Outcomes of Infective Endocarditis in Addicts and Non-Addicts

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Abstract:

Background: The prevalence of infective endocarditis has markedly increased in Egyptian population especially among intravenous drug addicts. Studies that link infective endocarditis and injection of drugs as a problematic social cause in our population still scarce and query and up to our knowledge this is the first study to discuss the clinical features and outcomes of infective endocarditis in addicts and non-addicts in our population.

Aim: To highlight on the features and outcomes of infective endocarditis in our Egyptian population especially in addict people.

Patients and methods: According to the modified Duke criteria, individuals who were diagnosed with "definite infective endocarditis" at the cardiology department of Zagazig University Hospital and the National Heart Institute were included in this observational cohort study. Patients were classified into two groups: group I: injection drug use-related infective endocarditis (IDU-IE) and group II: non-injection drug use-related infective endocarditis (Non IDU-IE). Clinical features and outcomes were evaluated.

Results: IDU-IE patients were significantly younger in age than those with non-IDU-IE with a statistically significant male gender predominance. S. aureus, fungal and polymicrobial infections were more significantly associated with IDU-IE patients. IDU-IE patients had a statistically significant longer hospital-stay, utilized a statistically significant more total number of antibiotics with longer duration of treatment and received a statistically significant less rates of cardiac surgery. The in-hospital, out-hospital and over-all mortality (in-hospital and out-hospital) was found to be significantly higher in IDU-IE than non-IDU-IE.

Conclusions: IE remains a highly morbid condition in Egyptian population. Our data suggest that although patients with IDU-IE are much younger and have fewer comorbid conditions, they need a greater number of antimicrobials, have longer hospital stay, still receive less surgical management than expected and suffer more pulmonary complications and higher mortality rates than a more at-risk non-IDU-IE cohort.

Keywords: Infective Endocarditis, addiction, Echocardiography.

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Introduction:

In 1885, Sir William Osler wrote in his third Gustonian lecture on infective endocarditis (IE) that "few diseases present greater difficulties in the way of diagnosis, difficulties which in many

cases are practically invincible" *(1)*. He had no idea that his thoughts would be applied more than 150 years later. There are many explanations for this shortage of research advancement. First of all, IE is unpredictable and uncommon. Nearly all body systems are involved in its clinical features, therefore the diagnosis is usually difficult to make. Second, there is insufficient evidence-based data because research has been conducted in a retrospective manner and relies only on the data of registries *(2)*. More than 3 decades ago, it was stated that "there is still as much art as science in the care of patients with endocarditis" *(3)*.

Infective endocarditis (IE) is severely morbid condition, has a high fatality rate and unfortunately is becoming more common worldwide *(4)*.

Although rheumatic heart disease, prosthetic valves and congenital heart abnormalities can make individuals at risk for IE, intravenous (I.V) drug use remains a major factor, increasing the risk of IE incidence a hundred times when compared with the general population *(5)*.

Abuse of intravenous drugs raises the risk of IE through a number of pathways, including direct damage from injected particles, poor injection hygiene, use of contaminated equipment, and drug-mediated physiological changes that result in vasospasm and cardiac injury. (*6*).

I.V. drug abuse-IE is more frequently right-sided due to particulate matter exposure, but non-IV drug abuse-IE is more frequently left-sided due to enhanced oxygenation and turbulence-mediated endothelial damage *(7)*.

The incidence of IE closely correlates with the rates of intravenous drug abuse. As I.V. drug abuse rates rise, the incidence rates of IE also increase *(8)*.

In spite of this relationship, few studies have inspected the injection drug use-IE (IDU-IE) population's outcomes and complications after acute hospitalization. Patients with IDU-IE are more frequently exposed to persistent endocarditis, subsequent valvular surgeries, and longer hospital stay periods than those with non-IDU-IE. The frequency and key reasons for readmissions after hospitalization for IDU-IE remain unclear *(9)*.

Therefore, our study is going to analyze clinical features and recent trends, complications, mortality, re-hospitalization and the need for surgery for IE in injection drug users (IDU-IE) compared with non-injection drug use IE (Non-IDU-IE).

Patients and Methods

This observational cohort study was conducted From October 2020 to November 2021, at the Cardiology Department, Zagazig University Hospital and the National Heart Institute. Each patient who survived was given an extended six-month follow-up following his release.

All patients who were diagnosed as "definite infective endocarditis" according to the modified Duke criteria were included in the study *(10)*. Definite IE diagnosis is based on 2 major criteria, or 1 major criterion and 3 minor criteria, or 5 minor criteria. Major criteria include; (blood culture positive for IE and imaging studies positive for IE), while minor criteria include (predisposition for IE, fever >38^{o}C, vascular phenomena, immunological phenomena and microbiological evidence no meeting major criteria) *(2)*.

All patients were subjected to the following; full history and clinical examination with focusing on risk factors for IE like rheumatic heart disease (RHD), congenital heart abnormalities (ASD, VSD, PFO, bicuspid aortic valve), presence of prosthetic valves or intracardiac device, renal dialysis, injection drug abuse or prior hospitalization for IE, age gender, presence of immune compromised diseases, presence of fever and its duration.

General examination focused on Specific vascular and immunological signs as: Osler nodules, Janeway lesions, splinter hemorrhage and Roth spots. Also, embolic complications such as stroke, splenic or hepatic abscesses, pulmonary embolism and peripheral embolization were considered. Local cardiac examination was carried out with focusing on auscultating to the heart with a stethoscope sound of a new heart murmur or a change in the sound of a previously existing heart murmur, extra heart sounds, the click of the prosthetic valves, cardiomegaly and signs of heart failure.

A twelve-lead ECG was done to all patients using a paper speed of 25 mm/s and standardization of 1mV/10 mm was analyzed for rhythm, conduction abnormality, chamber enlargement and development of arrhythmias or ischemic changes. Chest x-ray may show enlarged cardiac silhouette, pulmonary congestion, wedge-shaped opacity of pulmonary infarction, prosthetic valves or pleural effusion.

Blood culture was a cornerstone in the diagnosis and antibiotic treatment of IE; Three separate sets of blood cultures each from a separate venipuncture are obtained at least 1 hour apart over 24 hours. A follow up culture is obtained every 10 days till present of a negative one. The decision of discharge or referring to elective surgery was taken after 3 negative cultures. Other laboratory tests done included CBC, ESR, CRP, rheumatoid factor (RF) and serum creatinine.

Echocardiographic evaluation of patients (both Transthoracic Echocardiography “TTE” and Transesophageal Echocardiography “TEE”) was held using Philips iE33 and Philips Epiq7 ultrasound machines; manufactured by Philips Company in USA, using both TTE cardiac probe (S1-5) and TEE cardiac probe (X8-2t). Also, GE vivid E95 manufactured by General Electric company in USA using TTE cardiac probe (M5Sc) and TEE cardiac probe (6Tc). We focused on presence of vegetation with evaluation of site, size and mobility, presence of abscesses, pseudo-aneurysms, intra-cardiac fistulae and congenital lesions, valvular regurgitation and their degree (mild, moderate, moderately severe or severe), presence of dehiscence, rocking and para-valvular leak in case of prosthetic valve endocarditis and presence of pericardial effusion. Also, underlying cardiac problems were evaluated; rheumatic valve diseases, congenital heart defects and intracardiac pacemaker electrodes. TEE was performed in case of positive TTE finding of IE and also in case of negative TTE when there is a high index of suspicion for IE, particularly when TTE is of suboptimal quality. TEE standard views used for assessment of cardiac valves affected, vegetations, presence of abscesses, pseudo-aneurysms, congenital lesions and prosthetic valve complications due to IE.

The participants in our study were divided into two groups: group I included patients with injection drug use-related infective endocarditis (IDU-IE) and group II included patients with non-injection drug use-related infective endocarditis (Non IDU-IE).

Follow up:

The in-hospital mortality was 23 patients. So, the six-month follow up was obtained on the remaining **57 patients** who were followed up regarding the incidence of death, IE recurrence, stroke and heart failure.

Ethical approval:

Written consents were obtained according to research plan of our department after approval of the Institutional Review Board (IRB).

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 25. The following tests were done: independent-samples t-test, chi-square (X^2) test, The "Linear-by-Linear" test and Kaplan-Meier method.

Results:

Table (1): Comparison between the studied groups regarding the demographics and risk factors (n=80).

Demographics and risk factors	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
Age (years) mean ± SD (range)	38.8 ± 11.3 (18 – 64)	32.7 ± 7.5 (21 – 52)	42.1 ± 11.6 (18 – 64)	<0.001 (HS)
Male gender	56 (70%)	27 (96.4%)	29 (55.8%)	<0.001 (HS)
HTN	17 (21.3%)	3 (10.7%)	14 (26.9%)	0.091 (NS)
DM	13 (16.3%)	2 (7.1%)	11 (21.2%)	0.125 (NS)
Smoking	35 (43.8%)	16 (57.1%)	19 (36.5%)	0.076 (NS)
COPD	8 (10%)	3 (10.7%)	5 (9.6%)	1.0 (NS)
Rheumatic heart disease	45 (56.3%)	12 (42.9%)	33 (63.5%)	0.076 (NS)
Congenital heart disease	6 (7.5%)	3 (10.7%)	3 (5.8%)	0.417 (NS)
ASD	1 (1.3%)	0 (0%)	1 (1.9%)	1.0 (NS)
VSD	2 (2.5%)	1 (3.6%)	1 (1.9%)	1.0 (NS)
Bicuspid AV	3 (3.8%)	2 (7.1%)	1 (1.9%)	0.279 (NS)
Prosthesis or bio-prosthesis	17 (21.3%)	5 (17.9%)	12 (23.1%)	0.586 (NS)
Mechanical AV	10 (12.5%)	3 (10.7%)	7 (13.5%)	0.922 (NS)
Mechanical MV	5 (6.3%)	2 (7.1%)	3 (5.8%)	1.0 (NS)
Mitral bioprosthesis	2 (2.5%)	0 (0%)	2 (3.8%)	1.0 (NS)
Cardiac device	7 (8.8%)	2 (7.1%)	5 (9.6%)	1.0 (NS)

CKD	9 (11.3%)	0 (0%)	9 (17.3%)	0.023 (S)
Prior IE	10 (12.5%)	8 (28.6%)	2 (3.8%)	0.003 (S)
HCV	18 (22.5%)	8 (28.6%)	10 (19.2%)	0.340 (NS)
HIV	10 (12.5%)	10 (100%)	0 (0%)	<0.001 (HS)

Table (1) shows that group I patients were significantly younger in age than those of group II (p<0.001) with statistically significant male gender predominance (p<0.001). Regarding the risk factors and comorbidities, group I had a significant higher percentage of patients with prior IE (p=0.003). Also, all the 10 patients with HIV in our study population were included in group I (p<0.001). whereas, group II had a significant higher percentage of CKD patients than group I (p=0.023). No statistically significant difference was found between the two groups regarding other demographics and risk factors.

Table (2): Comparison between the studied groups regarding the clinical data (n=80).

Clinical data	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
Source of infection				
IV injection	35 (43.8%)	28 (100%)	7 (13.5%)	<0.001 (HS)
Dialysis	9 (11.2%)	0 (0%)	9 (17.3%)	0.023 (S)
Non-cardiac surgery	9 (11.2%)	0 (0%)	9 (17.3%)	0.023 (S)
Dental procedure	8 (10%)	0 (0%)	8 (15.4%)	0.045 (S)
Unknown	19 (26.3%)	0 (0%)	19 (36.5%)	<0.001 (HS)
Fever at time of admission				
Incidence of fever	60 (75%)	26 (92.9%)	34 (65.4%)	0.007 (S)
Duration (days)	16.5 ± 5.8	18.7 ± 6.2	14.7 ± 4.9	0.008 (S)
Symptoms and signs				
New or changed murmur character	46 (57.5%)	17 (60.7%)	29 (55.8%)	0.670 (NS)
Dyspnea	58 (72.5%)	18 (64.3%)	40 (76.9%)	0.227 (NS)
Chest pain	8 (10%)	2 (7.1%)	6 (11.5%)	0.706 (NS)
Syncope	5 (6.3%)	4 (14.3%)	1 (1.9%)	0.048 (S)
Neurological symptoms	12 (15%)	1 (3.6%)	11 (21.2%)	0.048 (S)
Weight loss	21 (26.3%)	13 (46.4%)	8 (15.4%)	0.003 (S)
Jaundice	18 (22.5%)	11 (39.3%)	7 (13.5%)	0.008 (S)
ECG				
Sinus rhythm	58 (72.4%)	23 (82.1%)	35 (67.3%)	0.521 (NS)
AF	13 (16.3%)	3 (10.7%)	10 (19.2%)	
AV block	3 (3.8%)	1 (3.6%)	2 (3.9%)	
Paced rhythm	6 (7.5%)	1 (3.6%)	5 (9.6%)	
Vascular phenomena				

Over-all	39 (48.8%)	14 (50%)	25 (48.1%)	0.870 (NS)
Pulmonary embolism	9 (11.3%)	8 (28.6%)	1 (1.9%)	0.001 (S)
Stroke	11 (13.8%)	1 (3.6%)	10 (19.2%)	0.086 (NS)
Conjunctival hemorrhage	4 (5%)	2 (7.1%)	2 (3.9%)	0.609 (NS)
Splinter hemorrhage	9 (11.3%)	2 (7.1%)	7 (13.5%)	0.483 (NS)
Janeway lesions	6 (7.5%)	1 (3.6%)	5 (9.6%)	0.659 (NS)
Immunological phenomena				
Over-all	13 (16.3%)	2 (7.1%)	11 (21.2%)	0.125 (NS)
Roth spots	3 (3.8%)	0 (0%)	3 (5.8%)	0.548 (NS)
Osler's node	5 (6.3%)	1 (3.6%)	4 (7.7%)	0.653 (NS)
Rheumatoid factor	5 (6.3%)	1 (3.6%)	4 (7.7%)	0.653 (NS)

Table (2) shows that IV lines were the most common source of infection in IE patients being the sole source in group I compared to patients of group II who got infected via many other sources ($p<0.001$). Regarding the presenting symptoms; patients within group I showed a significant higher incidence of fever than those of group II ($p=0.007$), also the duration of fever was significantly longer in group I than group II ($p=0.008$). Some symptoms were more statistically significant in group I than in group II like syncope ($p=0.048$), weight loss ($p=0.003$) and jaundice ($p=0.008$). Neurological symptoms appeared to be more statistically significant in group II than in group I ($p=0.048$). The remaining other symptoms; dyspnea, cough, chest pain or neurological symptoms showed no statistical difference between the two groups. Regarding the vascular phenomena, only pulmonary embolism was statistically significant in group I than in group II ($p=0.001$). Other vascular and immunological phenomena were comparable between the two groups.

Table (3): Comparison between the studied groups regarding the echocardiographic data (n=80).

Echocardiographic data	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
Presence of vegetations				
	77 (96.3%)	**28 (100%)**	**49 (94.2%)**	**0.548 (NS)**
Number of vegetations (n=77)				
Single	55 (71.4%)	21 (75%)	34 (69.4%)	0.600 (NS)
Multiple	22 (28.6%)	7 (25%)	15 (30.6%)	
Size of vegetations (n=77)				
<10 mm	30 (39%)	8 (28.6%)	22 (44.9%)	0.158 (NS)
≥10 mm	47 (61%)	20 (71.4%)	27 (55.1%)	
Site of vegetations (n=77)				
Mitral	25 (32.5%)	2 (7.1%)	23 (46.9%)	<0.001 (HS)
Aortic	24 (31.2%)	4 (14.3%)	20 (40.8%)	0.016 (S)

Tricuspid	26 (33.8%)	21 (75%)	5 (10.2%)	<0.001 (HS)
Pulmonary	3 (3.9%)	1 (3.6%)	2 (4.1%)	1.0 (NS)
Pacemaker lead (CDRIE)	7 (9.1%)	2 (7.1%)	5 (10.2%)	1.0 (NS)
IE side				
Left side	47 (58.7%)	5 (17.9%)	42 (80.2%)	<0.001 (HS)
Right side	31 (38.8%)	21 (75%)	10 (19.2%)	
Both sides	2 (2.5%)	2 (7.1%)	0 (0%)	
Prosthetic complications				
Over-all	14 (17.5%)	4 (14.3%)	10 (19.2%)	0.760 (NS)
Rocking	4 (5%)	1 (3.6%)	3 (5.8%)	1.0 (NS)
Dehiscence	7 (8.8%)	2 (7.1%)	5 (9.6%)	1.0 (NS)
Stuck valve	3 (3.8%)	1 (3.6%)	2 (3.8%)	1.0 (NS)
Other findings				
Aortic root abscess	10 (12.5%)	1 (3.6%)	9 (17.3%)	0.153 (NS)
Leaflet perforation	7 (8.8%)	2 (7.1%)	5 (9.6%)	1.0 (NS)
Pericardial effusion	15 (18.8%)	9 (32.1%)	6 (11.5%)	0.024 (S)

Table (3) shows that that presence vegetations was the hallmark and most frequent feature of IE in our patient's echocardiograms without significant difference between the two groups (p=0.548). Right sided vegetations showed a statistically significant association with group I patients, unlike the left sided ones that were significantly associated with group II (p<0.001). The same applies for the valve over which the vegetation is attached; the tricuspid valve being more significantly involved in group I than in group II (p<0.001). On the other hand, the mitral and aortic valves were more significantly involved in group II than in group I (p<0.001 and 0.016 respectively). Pericardial effusion was more significantly noticed in group I than group II (p=0.024). Other echocardiographic findings were comparable between the two groups without significant statistical difference.

Table (4): Comparison between the studied groups regarding the microbiological data (n=80).

Microbiological data	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
BCNIE				
	16 (20%)	2 (7.1%)	14 (26.9%)	0.035 (S)
Causative pathogen				
Staphylococci	**23 (28.8%)**	**12 (42.9%)**	**11 (21.2%)**	**0.041 (S)**
S. aureus	16 (20%)	10 (32.1%)	6 (11.5%)	0.010 (S)
CoNS	7 (8.8%)	2 (7.1%)	5 (9.6%)	1.0 (NS)
Streptococci	**10 (12.5%)**	**1 (3.6%)**	**9 (17.3%)**	**0.153 (NS)**

S. viridans	7 (8.8%)	1 (3.6%)	6 (11.5%)	0.412 (NS)
S. bovis	3 (3.8%)	0 (0%)	3 (5.8%)	0.548 (NS)
Enterococci (E. faecalis)	**6 (7.5%)**	**1 (3.6%)**	**5 (9.6%)**	**0.659 (NS)**
HACEK	**5 (6.3%)**	**2 (7.1%)**	**3 (5.8%)**	**1.0 (NS)**
Hemophilus	1 (1.25%)	1 (3.6%)	0 (0%)	1.0 (NS)
Actinobacillus	2 (2.5%)	0 (0%)	2 (3.8%)	1.0 (NS)
Cardiobacterium	1 (1.25%)	1 (3.6%)	0 (0%)	1.0 (NS)
Eikenella	0 (0%)	0 (0%)	0 (0%)	1.0 (NS)
Kingella	1 (1.25%)	0 (0%)	1 (1.9%)	1.0 (NS)
Gram -ve rods	**8 (10%)**	**1 (3.6%)**	**7 (13.5%)**	**0.250 (NS)**
Klebsiella	4 (5%)	1 (3.6%)	3 (5.8%)	1.0 (NS)
E. coli	2 (2.5%)	0 (0%)	2 (3.8%)	0.539 (NS)
P. aeruginosa	2 (2.5%)	0 (0%)	2 (3.8%)	0.539 (NS)
Fungal infection	**7 (8.8%)**	**5 (17.9%)**	**2 (3.8%)**	**0.048 (S)**
Candida	5 (6.3%)	3 (10.7%)	2 (3.8%)	0.337 (NS)
Aspergillus	2 (2.5%)	2 (7.1%)	0 (0%)	0.120 (NS)
Polymicrobial infection	**5 (6.3%)**	**4 (14.3%)**	**1 (1.9%)**	**0.048 (S)**

Table (4) shows that group I had a significant higher incidence of blood culture negative infective endocarditis (BCNIE) than group I (p=0.035). Staphylococci were the most common causative pathogen in patients with positive blood cultures, group I cultures showed more statistically significant isolations of staphylococci than group II (p=0.041). There was also a predominance of s. aureus, that was also significantly more found in group I cultures than in group II (p=0.010). Also, fungal endocarditis showed more statistically significant prevalence in group I than group II (p=0.048). Polymicrobial infection was significantly more frequent in group I than in group II (p=0.048). other causative pathogens didn't show significant difference between the two groups.

Table (5): Comparison between the studied groups regarding the antimicrobial data (n=80).

Antimicrobial data	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
Basis of anti-microbial choice				
Culture/Serology based	48 (60%)	26 (92.9%)	38 (73.1%)	0.035 (S)
Empirical	16 (20%)	2 (7.1%)	14 (26.9%)	
Total number of antimicrobials used				
Two	27 (33.8%)	4 (14.3%)	23 (44.2%)	0.007 (S)
Three	46 (57.5%)	20 (71.4%)	26 (50%)	
More than three	7 (8.8%)	4 (14.3%)	3 (5.8%)	
Duration of anti-microbial treatment (weeks)				
Mean ± SD	4.2 ± 1.8	6.4 ± 2.3	2.8 ± 1.3	0.009 (S)

Table (5) shows a significant difference among the two groups regarding the basis of antimicrobial treatment choice (p=0.035); as group I patients received statistically significant more culture/serology based antibiotic therapy than group II ones. Also, group I patients utilized a statistically significant more total number of antibiotics than group II (p=0.007) with longer duration of treatment (p=0.009).

Table (6): Comparison between the studied groups regarding the in-hospital complications (n=80).

In-hospital complications	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
Severe sepsis	20 (25%)	10 (35.7%)	10 (19.2%)	0.104 (NS)
Heart failure	19 (23.8%)	6 (21.4%)	13 (25%)	0.720 (NS)
Acute valvular regurgitation	17 (21.3%)	4 (14.3%)	13 (25%)	0.264 (NS)
Prosthetic complications	14 (17.5%)	4 (14.3%)	10 (19.2%)	0.760 (NS)
Renal failure	7 (8.8%)	3 (10.7%)	4 (7.7%)	0.691 (NS)
Septic pulmonary embolism	10 (12.5%)	8 (28.6%)	2 (3.8%)	0.003 (S)
Coronary embolism	2 (2.5%)	0 (0%)	2 (3.8%)	0.539 (NS)
Splenic abscess or infarction	5 (6.3%)	2 (7.1%)	3 (5.8%)	1.0 (NS)
Mycotic aneurysm	4 (5%)	1 (3.6%)	3 (5.8%)	1.0 (NS)
Stroke	10 (12.5%)	1 (3.6%)	9 (17.3%)	0.153 (NS)

Table (6) shows that the incidence of in-hospital complications was high in our study population. Septic pulmonary embolism showed a statistically significant higher incidence in group I than group II (p=0.003). Other complications showed no statistically significant difference between the two groups.

Table (7): Comparison between the studied groups regarding the in-hospital course (n=80).

In-hospital course	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	80	28	52	
Hospital-stay duration (days)				
Mean ± SD	24.2 ± 8.7	27.0 ± 9.1	22.7 ± 8.2	0.035 (S)
In-hospital fever duration (days)				
Mean ± SD	15.8 ± 5.2	17.0 ± 4.7	14.9 ± 5.4	0.116 (NS)
In-hospital outcomes				
Response to medical treatment	42 (52.5%)	12 (42.9%)	30 (57.7%)	0.205 (NS)

Need surgery	63 (78.8%)	20 (71.7%)	43 (82.7%)	0.240 (NS)
Surgery performed	**43 (68.3%)**	**10 (50%)**	**33 (76.7%)**	0.034 (S)
Surgery not performed	20 (31.7%)	10 (50%)	10 (23.3%)	
Type of surgery	**N=43**	**N=10**	**N=33**	
Lead extraction	3 (7%)	1 (10%)	2 (6.1%)	0.408 (NS)
MVR	11 (25.6%)	0 (0%)	11 (33.3%)	0.043 (S)
AVR	9 (20.9%)	1 (10%)	8 (24.2%)	0.659 (NS)
DVR	10 (23.3%)	1 (10%)	9 (27.3%)	0.407 (NS)
TV replacement	8 (18.6%)	7 (70%)	1 (3%)	<0.001 (HS)
Bentall	2 (4.7%)	0 (0%)	2 (6.1%)	1.0 (NS)
In-hospital mortality and causes of death				
In-hospital mortality	23 (28.7%)	12 (42.9%)	11 (24.2%)	0.041 (S)
Sepsis/multi-organ failure	6 (26.1%)	4 (33.3%)	2 (18.2%)	0.640 (NS)
Cardiovascular	17 (73.9%)	8 (66.7%)	9 (81.8%)	
Heart failure	8 (34.8%)	2 (16.7%)	6 (54.5%)	0.089 (NS)
Arrhythmias	2 (8.7%)	1 (8.3%)	2 (18.2%)	1.0 (NS)
Pulmonary embolism	6 (26.1%)	5 (41.7%)	1 (9.1%)	0.155 (NS)
Cerebral embolism	1 (4.3%)	0 (0%)	1 (9.1%)	0.478 (NS)

Table (7) shows that group I patients had a statistically significant longer hospital-stay than those of group II (p=0.035). Group I patients received a statistically significant less rates of surgery than group II (p=0.034). Regarding the type of surgery performed, group I patients were more likely to receive a tricuspid valve replacement (p<0.001) and less likely to receive mitral valve replacement (p=0.043). Although the in-hospital mortality was significantly higher in group I than in group II (p=0.041), the causes of mortality mentioned didn't show a statistically significant differences between the two groups.

Table (8): Comparison between the studied groups regarding the six-month follow-up (n=57).

6-month follow-up	Total	Group I (IDU-IE)	Group II (Non IDU-IE)	P-value
Count	57	16	41	
Follow-up outcomes				
Composite end-point	**20 (35.1%)**	**8 (50%)**	**12 (29.3%)**	**0.141 (NS)**
Recurrent IE	3 (5.3%)	1 (6.3%)	2 (4.9%)	1.0 (NS)
Heart failure	4 (7%)	1 (6.3%)	3 (7.3%)	1.0 (NS)
Stroke	6 (10.5%)	2 (12.5%)	4 (9.8%)	1.0 (NS)
Death	7 (12.3%)	4 (25%)	3 (7.3%)	0.048 (S)
Over-all mortality (in-hospital and out-hospital), n=80				
Count	**80**	**28**	**52**	
Total deaths	30 (37.5%)	16 (57.1%)	14 (26.9%)	0.008 (S)

Table (8) shows that there was no statistical difference regarding the composite end-point between group I and group II (p=0.141). Out-hospital death rate was significantly higher in group I than group II (p=0.048). The other endpoints (hospitalization for recurrent IE, heart failure and stroke) did not show a statistically significant difference between the two groups. At the end of the follow-up period, the over-all mortality (in-hospital and out-**hospital)** was found to be significantly higher in group I than in group II (p=0.008).

Figure 1 shows Kaplan-Meier estimates for survival analysis (Log rank test, p=0.044); the IDU-IE patients showed a significant higher risk of mortality than non-IDU-IE patients during the 6-month follow-up period (25% vs. 7.3%; adjusted Hazard Ratio:1.87; 95% CI, 1.22-4.23).

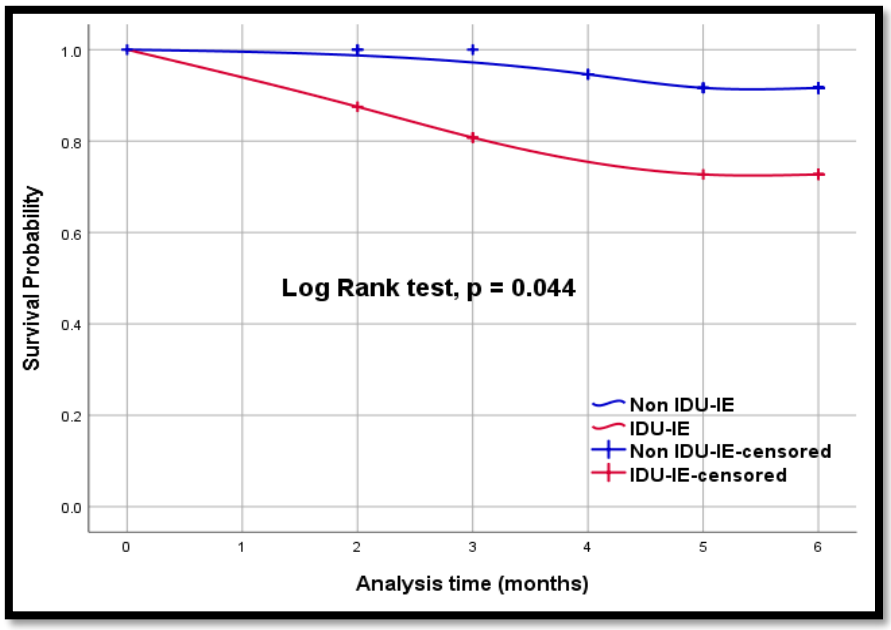

Figure (1): Kaplan-Meier survival curve for 6-month mortality in both groups (IDU-IE vs. Non IDU-IE) during the 6-month follow-up

Discussion:

In this study, there are numerous health differences between individuals with infective endocarditis related to injection drug use (IDU-IE) and individuals without such a condition (non-IDU-IE). Patients with IDU-IE were younger and had fewer comorbidities than patients with non-IDU-IE, but they nonetheless experienced equal or greater rates of emergency department visits, the need for heart surgery, and mortality.

Regarding the age, people with IDU-IE in our study were more likely to be younger (mean age 32.7 vs. 42.1 years, $p < 0.001$) with male predominance (96.4% vs. 55.8%, $p < 0.001$) and prior IE (28.6% vs. 3.8%, $p = 0.003$) compared to those with non-IDU-IE, reflecting the current trends of the addiction demographics. Similarly, ***Wurcel et al. (6)*** that examined the patterns in IDU-IE hospital admissions observed a move toward higher proportions in younger

demographics. When they looked at the IDU-IE as a whole, they also discovered that the female gender was less prevalent (female = 40.9%). Also, ***Leahey et al. (11)*** the median age of patients with IDU-IE was 33 (interquartile range [IQR], 26-44) compared to 63 (IQR, 53-74) in non-IDU-IE (p 0.001), and the percentage of patients with prior IE was (21% vs. 7%, p 0.001). In contrast, their study revealed that there were more women with IDU-IE (46% vs. 30%), which could be attributed to the fact that women in our oriental societies have less of an addiction problem.

Our study showed that people with IDU-IE had higher prevalence of HIV; 10 patients out of the of the 28 IDU-IE patients had HIV, no HIV cases in non IDU-IE were found (35.7% vs. 0%, $p < 0.001$). The high prevalence of HIV among IDU-IE patients highlights the importance of HIV testing in this cohort as well as linking patients to outpatient HIV care after being admitted with infective endocarditis. According to a recent study conducted in South Africa, ***Meel and Essop (12)*** reported demographic findings like ours. It showed increase in the incidence of IE related to IDU amongst Africans. These were young aged (mean age; 25.8 years), predominantly male (97.1%) and majority were HIV infected (76.1%).

In our study, IDU-IE patients showed more significant incidence of fever (92.9% vs. 65.4%, $p = 0.007$) with longer duration (mean duration 18.7 vs. 14.7 days, $p = 0.008$) than those with non-IDU-IE. These findings are in agreement with ***Damlin and Westling (13)*** that showed a non-significant but still higher incidence of fever in IDU-IE than non-IDU-IE (91% vs. 85%, $p = 0.07$).

Our study showed that staphylococci were the predominant organisms in patients with positive blood cultures (28.8%), and much more frequently found in patients with IDU-IE cultures than those with non-IDU-IE (42.9% vs. 21.2%, $p = 0.041$). Also, our non-IDU-IE patients were significantly older and showed significantly higher percentage of negative blood cultures than those with IDU-IE (26.9% vs. 7.1%, $p = 0.035$). This agrees with a study by ***DeSimone et al. (14)*** who showed that euthermic endocarditis (IE with temperature ≤ 38.0° C) tends to occur in older age ($p = 0.001$). It also found a significant association between euthermic endocarditis and the type of causative microorganisms isolated from blood cultures ($p < 0.001$). In particular, patients with IE caused by S. aureus tended more likely to be febrile while patients with culture-negative IE were more likely to be euthermic.

We also noted some other symptoms had a higher significant incidence in patients with IDU-IE than those with non-IDU-IE like syncope (14.3% vs. 1.9%, $p = 0.048$), weight loss (46.4% vs. 15.4%, $p = 0.003$) and jaundice (39.3% vs. 13.5%, $p = 0.008$).

Regarding syncope, its higher incidence in IDU-IE patients through different mechanisms according to the addicted material. ***Chen and Ashburn (15)*** demonstrated that opioids can induce histamine release, causing vasodilation and increased capillary permeability, resulting in blood pressure reduction, orthostatic hypotension and syncope. ***Behzadi et al. (16)*** attributed the incidence of syncope to the prolongation of the QT interval and development of torsades de pointes (TdP) produced by opioids abused like methadone, tramadol and oxycodone.

Moreover, the significant higher incidence of jaundice and weight loss in IDU-IE patients. ***Shmueli et al. (17)*** explained this by more affection of the tricuspid valve in these patients leading to perforation, destruction, development of severe tricuspid regurgitation and right-side heart failure with increased the incidence of systemic congestion causing hepatic congestion and jaundice, gastric mucosal congestion with dyspepsia and anorexia.

In our study, the proportion of right sided infective endocarditis was higher among the IDU population than non-IDU ones (75% vs. 17.2%, $p < 0.001$). Accordingly, the most affected valve was the tricuspid valve in IDU-IE patients (75% vs. 10.2%, $p < 0.001$), whereas the mitral valve was the most affected valve of non-IDU-IE population (46.9% vs. 7.1%, $p<0.001$) followed by the aortic valve (40.8% vs. 14.3%, $p=0.016$). This is consistent with most of the prior literatures, for example ***Pericàs et al. (18)*** showed significant higher involvement of tricuspid valve in IDU-IE than non-IDU-IE (56.2% vs. 18.3%, $p < 0.001$). On the other hand, both aortic and mitral valves were more significantly involved in non-IDU-IE ($p < 0.001$ and 0.007, respectively).

In our study, pericardial effusion was significantly more prevalent in patients with IDU-IE (32.1% vs. 11.5%, $p = 0.024$). This result agrees with ***Regueiro et al. (19)*** who reported that patients with pericardial effusion had a greater prevalence of intravenous drug use (38% vs 23%, $p = 0.004$) and more frequent right-sided IE than patients without pericardial effusion (33% vs 17%, $p = 0.019$). Also, a study conducted by ***Firouzi et al. (20)*** demonstrated that pericardial effusion was more prevalent in patients with right-heart involvement (65% in right-heart IE vs 50% in left-heart IE; $p = 0.002$). The development of pericardial effusion in IDU with IE may be secondary to proinflammatory status and immune response in IE. However, analysis of pericardial fluid would be necessary to confirm this hypothesis. On the contrary, a study by ***Youssef et al. (21)*** who compared IE patients with pericardial effusion with IE patients without pericardial effusion; they found that IE patients with pericardial effusion, had more left-sided vegetation (55.6% vs 77.3%, $p < 0.001$), taking into account that more than 20% of their study population showed renal impairment which could be a predisposing factor for the incidence of pericardial effusion.

Bacteria from the skin or injection tools such syringes, needles, cookers, cottons, and water can enter the bloodstream and cause IDU-IE. As a result, numerous species, including bacteria and fungi, are involved in IDU-IE. Our study showed that staphylococci were the main causative organisms in our study population (28.8%) being more significantly detected in the blood cultures of IDU-IE group (42.9% vs. 21.2%, $p=0.041$). This agrees with ***Kadri et al. (22)*** -whose study included more than 950 thousand of infective endocarditis patients- showed that staphylococcus species were the most common organisms identified in drug abuse related IE group when compared with the non-drug abuse IE one (47.2% vs. 22.1%, $p < 0.001$). ***Pericàs et al. (18)*** -whose study included more than 7500 patients- demonstrated the same as staphylococci were much more significantly found in cultures of patients with IDU-IE than non-IDU-IE ones ($p < 0.001$). The two previously mentioned studies showed no significant difference between the addicts and non addicts with IE regarding fungal infection, our study showed fungi (Aspergillus

and Candida) were more significantly detected in the IDU-IE group cultures (17.9% vs. 3.8%, p=0.048). A recent study by ***Caceres et al. (23)*** agreed with our study concerning more fungi being detected in cultures of IDU related IE than non-IDU ones (9.6% vs. 2.2%, p = 0.003).

Our study also found that IE caused by multiple organisms "polymicrobial IE" was significantly more frequent in IDU-IE group than in non-IDU-IE one (14.3% vs. 1.9%, p=0.048). This finding is in concordance with ***Sousa et al. (24)*** who demonstrated that polymicrobial endocarditis occurs primarily in IDUs compared with non-drug misusers, generally due to staphylococcal, streptococcal and pseudomonal infection. ***Pericàs et al. (18)*** partly agreed with ours as they found that IDUs had higher -but statistically insignificant- incidence of polymicrobial IE than non-IDUs (2.7% vs. 1.6%, p=0.115).

Blood culture negative infective endocarditis (BCNIE) is an important entity, 20% of our study population showed negative blood cultures. The non-IDU-IE group showed more significant percentage of negative blood cultures than the IDU-IE patients (26.9% vs. 7.1%, p = 0.035). This copes with ***Pericàs et al. (18)*** who found that BCNIE represented 7.5% in non-IDU-IE vs. 3.4% in IDU-IE, p < 0.001. On the contrary, another two studies; ***Leahey et al. (11)*** and ***Caceres et al. (23)*** showed non-significant but still more prevalent culture negative endocarditis in non-IDU-IE than patients with IDU-IE (p = 0.10 and 0.17 respectively).

Regarding the antimicrobial therapy used, IDU-IE patients in our study were shown to utilize a significant more total number of antibiotics (p = 0.007) and longer duration of antibiotics treatment (p=0.009) than non-IDU-IE ones. This could be explained by the polymicrobial nature of IE in injection drug users, more resistant species to antibiotics and also the high prevalence of fungal infection in these patients.

The overall incidence of in-hospital complications is high in our study population in both groups. No statistically significant difference was found between patients with IDU-IE and non-IDU-IE except for septic pulmonary embolization that was found to be significantly more frequent in IDU-IE patients (28.6% vs. 3.8%, p=0.003). Septic pulmonary embolism was also statistically the most frequent vascular phenomenon diagnosed in IDU-IE patients at presentation when compared with non-IDU-IE patients (28.6% vs. 0%, p<0.001). This agrees with ***Bui et al. (25)*** Our study consisted of roughly 90,000 hospital admissions for IE patients. 15,490 (17%) of these hospitalizations were connected to drug usage. The risk of pulmonary consequences was highest in drug-use IE (DU-IE) (OR 2.97, 95% CI 2.50, 3.45). The number of IE patients with at least one pulmonary consequence was 6,580 (7%) patients. Pyothorax (3% vs. 1%, p 0.001), lung abscess (3% vs. 1%, p 0.001), and septic pulmonary embolism (27% vs. 2%, p 0.001) were diagnoses that were more frequently associated with DU-IE hospitalizations. Also, ***Pericàs et al. (18)*** showed the same finding regarding pulmonary emboli incidence (30.6% for IDU-IE vs. 4.2% for non-IDU-IE, p < 0.001). The higher incidence of right-sided valve dysfunction linked to intravenous drug use may be a significant factor in explaining the higher incidence of pulmonary problems seen in IDU-IE patients compared to non-IDU-IE patients.

We found that IDU-IE patients had significantly longer period of hospital stay than non-IDU-IE ones (mean days; 27 vs 22.7, p = 0.035). this agrees with many studies that showed similar results regarding the hospital stay length. A study by ***Rudasill et al. (26)*** that included more than 120.000 IE patients demonstrated that IDU-IE was associated with significant increase in the length of hospital stay relative to non–IDU-IE (mean days; 18.5 vs 14.4, p < 0.001). ***Gray et al. (27) and Bui et al. (25)*** both also showed longer hospital stay IDU-IE than non-IDU-IE (p = 0.001 and <0.001 respectively).

The IDU-IE group had a significantly lower incidence of patients who were actually operated on (50% vs. 67.7%, p = 0.034), despite the fact that our study did not find a statistically significant difference between IDU-IE and non-IDU-IE patients regarding the requirement for surgical intervention (71.7% vs. 82.7%, p=0.240). This agrees with ***Pericàs et al. (18)*** who showed that surgical rates were overall higher in non-IDU-IE patients (39.5% vs. 47.8%; p < 0.001). ***Damlin and Westling (13)*** also had significantly less of the IDU-IE patients were treated with surgery; 27 (16%), compared with 121 (34%) among the non-IDU-IE patients (p < 0.01). In contradiction with this result, ***Rudasill et al. (26)*** found that patients with IDU-IE received valve surgery at equivalent rates to patients with non-IDU-IE (11.5% vs. 11.2%; p = 0.420). Their study also showed that patients with IDU-IE were more likely to receive a tricuspid valve procedure (2.8% vs. 0.9%; p < 0.001) and less likely to receive a mitral (4.9% vs. 6.0%; p < 0.001) or aortic (5.4% vs. 6.9%; p < 0.001) valve procedure that is interestingly agrees with ours; we found that patients IDU-IE were more likely to receive a tricuspid valve replacement (70% vs. 3%, p<0.001) and less likely to receive mitral valve replacement (0% vs. 33.3%, p=0.043). Because they are younger people with potentially less comorbidities and greater cardiopulmonary reserve, the delay in their identification of IE may help to explain why IDU-IE patients require less surgical intervention. Additionally, cardiothoracic surgeons are more likely to turn them away if they are in poor general health and have severe sepsisPatients who take drugs could also put off getting treatment. This characteristic could explain why this group of patients requires more time before cardiac surgery than non-IDU-IE patients. ***(28)***. Furthermore, patients with IDU-IE are more likely to develop tricuspid valve insufficiency, which is more tolerable than aortic and mitral valve insufficiencies with non-IDU-IE. ***(29)***.

Our study showed that the in-hospital mortality was significantly higher in IDU-IE group than non-IDU-IE one (42.9% vs. 24.2%, p = 0.041). This could be explained by being late for seeking medical care, delayed diagnosis and presentation, longer time to cardiac surgery and staphylococci being the predominant causative microorganism and most resistant to antibiotics. This result agrees with ***Marques et al. (30)*** multivariate analysis that demonstrated that one of the independent predictors of in-hospital mortality of IE was staphylococcus aureus etiology (OR 6.47; 95% CI: 1.07-39.01; p = 0.042) which is the predominant pathogen of IDU-IE patients in our study. Some other studies showed the opposite finding to ours regarding the in-hospital mortality. Univariate analysis by ***Rudasill et al. (26)*** showed that IDU-IE was associated with reduced mortality (6.8% vs. 9.6%; p<0.001), but no significant increase in the risk of mortality for IDU-

IE cases relative to non–IDU-IE cases was found after adjustment of odds ratio. Also, ***Pericàs et al. (18)*** showed that in-hospital mortality was lower in PWID compared with non-PWID (10.8% vs. 18.2%; p < 0.001). Whereas, both ***Leahey et al. (11) and Damlin and Westling (13)*** showed comparable in-hospital mortality rates among patients with IDU-IE and those with non-IDU-IE [(6% vs. 9%; p = 0.32) and (4% vs. 8%; p = 0.15) respectively].

During the 6-month follow-up period, both IDU-IE and non-IDU-IE patients showed non-significant difference regarding the composite endpoint; (50% vs. 29.3%; p = 0.141); However, the IDU-IE group still have a significant higher out-hospital (25% vs. 7.3%; adjusted Hazard Ratio:1.87; 95% CI, 1.22-4.23; survival analysis Log rank, p = 0.044) and overall mortality -in-hospital and out-hospital- when compared with the non-IDU group (57.1% vs. 26.9%; p = 0.008). Our result regarding the 6-month follow-up mortality is inconsistent with ***Pericàs et al. (18)*** who found that the overall 6-month mortality rates were 14.4% and 22.2% for IDU-IE and non-IDU-IE patients, respectively (p < 0.001). Another two studies that calculated mortality rates over different periods of time showed no significant difference in mortality rates between IDU-IE patients and non-IDU-IE ones. The first of them is ***Gray et al. (27)*** that found no significant difference of 90-day mortality between IDU-IE and non-IDU-IE (21.8% vs. 29.3%, p = 0.3). the other one is ***Leahey et al. (11)*** that showed slightly higher but still non-significant one-year mortality rate in IDU-IE patients when compared with non-IDU-IE (16% vs. 13%; p = 0.52) We could justify why our findings regarding the follow-up mortality contradict theirs by having a smaller sample size and lower rates of surgical intervention in the IDU-IE population.

Conclusions:

In conclusion, IDU-IE patients tend to have IE more frequently than other patients, making it a highly morbid illness. Our data suggest that although patients with IDU-IE are much younger and have fewer comorbid conditions, they need a greater number of antimicrobials, have longer hospital stay, still receive less surgical management than expected and suffer more pulmonary complications and higher mortality rates than a more at-risk non-IDU-IE cohort.

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