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Clinical Outcome in down Syndrome Children with Congenital Heart Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Author HMM designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author MHN contributed to the study design, author TS managed the literature searches, analyses of the study and author MD wrote the first draft of the manuscript and did part of analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Down syndrome (DS) is the most common chromosome abnormality among live born infants. The aim of this study is to determine the Clinical outcome of patients with DS and congenital heart disease (CHD).
Study Design: A cross-sectional study.
Place and Duration of Study: On 100 patients with DS and CHD who underwent diagnostic and therapeutic work up in the pediatric cardiology department from September 2001 through

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September 2012 in Imam Reza hospital (Mashhad, Iran).
Methodology: All data collected according to a designed checklist. Most of these patients had previous history of admission in the pediatric cardiology ward. Some of these data were derived from the patient's file. Others data got by taking a history from the parents of patients and direct follow up of the patients by pediatric assistant and echocardiography by a pediatric cardiologist. Surgery was done in Imam Reza hospital. Palliative surgeries include Pulmonary Artery Banding (PAB) +/- PDA closure (if the PDA was present) and total corrections include complete correction of the defect such as ASD closure, VSD closure and repair of other defects. Medical treatments include Digoxin, Captopril, Sildenafil and Propranolol which were administered based on the type of disorders. Independent t-test, and Chi-square test were used to compare quantitative and qualitative variables between groups, respectively. Data analysis was done with SPSS ver. 11.5 and $P<0.05$ was considered as statistically significant.
Results: The mean age of CHD diagnosis was 3.10±2.52 months and mean age of refer to pediatric cardiologist was 5.46±8.60 months. 52% of subjects were females. 50 patients underwent surgical therapy and 50 patients underwent non-surgical therapy (Medical therapy). Of 100 patients, 43(43%) patients were expired, 36(36%) patients had improved signs, and complications were detected in 25(43.85%) of live patients. The mean age of death in patients was 15.24±11.69 months. The Pulmonary Arterial Pressure (PAP) decreased in 68.4 percent of patients after surgical therapy and 16.6 percent of patients with non-surgical therapy. There is a significant correlation between the type of therapy and PAP after treatment (P=.001). Complications of CHD were detected in 8 patients of the surgical group (27.58% of live patients), 5(33.33%) patients of non-surgical (Medical therapy) group and in 12(92.3%) the refusing surgery group.
Conclusion: The early diagnosis and therapeutic intervention especially cardiac surgery is critical in this group.

Keywords: Down syndrome; congenital heart disease; clinical outcome.

1. INTRODUCTION

Down syndrome (DS) is the most common chromosome abnormality among live born infants [1]. The phenotype of DS is characterized by more than 80 clinical features, including cognitive impairments, muscle hypotonia, short stature, facial dysmorphisms, congenital heart disease, and several other anomalies. These clinical features can vary considerably in number and in severity, and some abnormalities, such as leukemia and Hirschsprung disease, occur at higher frequencies in patients with DS than in the general population [2]. Affected individuals are more prone to Congenital heart disease (CHD), gastrointestinal (GI) anomalies, leukemia, Alzheimer disease, immune dysfunction, hypothyroidism, diabetes mellitus, and problems with hearing and vision [3,4].

Indeed CHDs are considered to be the most important clinical phenomenon of DS as they contribute to significant morbidity and mortality. The prevalence of congenital heart abnormalities in patients with Down syndrome ranges from 40 to 50% and the most cardiac impairment in DS is because of endocardial cushion defects, include many defects characterized by involvement of the atrial septum, the ventricular septum, and one or both of the atrioventricular (AV) valves [5]. The most common heart defect seen in infants with DS is an AVSD. Other heart defects seen in infants with DS include VSD, ASD, and PDA [6].

Over recent decades, there has been a substantial raise in the life expectancy of children with DS with an improvement in average life expectancy from 12 years in the 1940s to 60 years today. This raise in life expectancy has mainly been due to the successful early surgical treatment of CHD in children with DS [7-9].

Management of DS requires an organized approach to ongoing evaluation and monitoring for associated abnormalities and prevention of common disorders.

The approach to the care of patients with DS and congenital heart diseases has changed over time. In the past, surgical repair of cardiac defects often was not considered, because of the long-term natural history and reduced life expectancy and because of reports that suggested higher perioperative morbidity and mortality rates. Higher postoperative infection rates, prolonged ventilation, and longer lengths of stay were reported for patients with DS. Higher mortality rates also were reported. In the past 3

decades, however, life expectancy and treatment for no cardiovascular morbidities in patients with DS, such as respiratory and neurodegenerative complications, have improved. During this time, outcomes for patients undergoing CHD surgery also have improved, because of refinements in surgical techniques and improvements in perioperative care. Surgical repair of CHD in patients with DS is now performed routinely. The decision to perform surgical repair earlier for patients with DS may be about the upper airway and feeding/growth issues associated with DS, besides poor growth and respiratory symptoms associated with congestive heart failure. Alternatively, concern regarding the development of early pulmonary vascular disease in patients with DS with cardiac defects involving significant left-to-right shunts may contribute to the earlier surgical intervention. It is known that factors such as pulmonary hypertension can be associated with a significant mortality risk in the patients [10]. Considering economic and social burden of this disease in all the communities, especially in developing countries, the aim of this study is to determine the clinical outcome of patients with DS and congenital heart disease.

2. MATERIALS AND METHODS

This is a cross-sectional study on 110 patients with DS and CHD over a ten year period from September 2001 through September 2012. The Inclusion and Exclusion criteria were:

The inclusion criteria were: Patients with DS and CHD who underwent diagnostic and therapeutic work up in the pediatric cardiology department in an educational hospital of Mashhad (A metropolitan in northeast of Iran) from September 2001 to 2012.

The exclusion criteria were: Patients who were not referred for follow up, Age older than 18 years old and Death before the treatment.

Of these patients, 10 cases had exclusion criteria and 100 patients were in this study. All data collected according to a designed checklist. Most of these patients had previous history of admission in the pediatric cardiology ward. Some of these data were derived from the patient's file. Others data got by taking a history from the parents of patients and direct follow up of the patients by pediatric assistant and echocardiography by a pediatric cardiologist.

Surgery was done in an educational hospital (Imam Reza). Palliative surgeries include Pulmonary Artery Banding (PAB) +/- PDA closure (if the PDA was present) and total corrections include complete correction of the defect such as ASD closure, VSD closure and repair of other defects.

Medical treatments included Digoxin, Captopril, Sildenafil and Propranolol which were administered based on the type of disorders.

Echocardiographic device is VIVID 7, which is made by GE Company with multi frequency probe (3-5 mHTZ) and the Angiographic device is Siemens monoplane.

In this study, statistical tables and charts were used to describe subject data. Quantitative variables such as birth weight and age of diagnosis were analyzed by independent t-test, and the Chi - square test was used to compare qualitative variables between groups. Data analysis was done with SPSS ver. 11.5 and $p<0.05$ was considered as statistically significant.

3. RESULTS AND DISCUSSION

One hundred patients with a diagnosis of CHD and DS were evaluated. Subjects were children from birth to 14 years old.

The mean age of CHD diagnosis was 3.10±2.52 months and mean age of referral to pediatric cardiologist was 5.46±8.60 months. Fifty two percent of subjects were females. The average birth weight of the subjects was 2744.8±522.83 gr (Range=1200 to 4900 gr). Sixty five percent of subject birth weight was in the range of 2500-3500 gr.

28% of patients were small for gestational age (SGA) and 7% had birth weight over than 3500 gr. Only 2 patients (2%) were large for gestational age (LGA).

Clinical signs/reasons for referral of patients to cardiologist are shown in Table-1.

As it is shown, only less than 20% of patients were referred to pediatric cardiologist because of down phenotype.

Pattern of CHD among studied population is shown in Table-2.

Also 27 patients had valvular heart disease (13 Aortic Insufficiency (AI), 7 Mitral Regurgitation (MR), 5 Pulmonary Insufficiency (PI) and 2 Pulmonary Stenosis (PS)) and 22 cases had a PFO. (5 cases of AVSD had Partial AVSD and another 31 cases had Complete AVSD)
Pattern of CHD based on treatment is shown in Table 3.

Surgical treatment was recommended for 82 of 100 patients. 50 of them underwent surgical therapy and 32 patients refused surgery, so fifty patients underwent non-surgical therapy.

In surgical group palliative surgery was done in 36(72%) patients and all them were a candidate for total correction, but only 6(16.66%) of them were referred for second surgery.

Total correction was done for 20 patients, which was one stage surgery in 14(70%) and two stages in 6 patients (30%).

Mean age of palliative surgery was 12.6 months (between 1 and 86 months) and mean age of total correction was 37.5 months (4.5 and 96 months).

Of 100 patients, 43(43%) patients were expired, which 21 of death was in surgical group and22 in the medical treatment group, 36(36%) patients had improved signs and complications were detected in 25(43.85%) of live patients.

The mean age of death in patients was 15.24±11.69 months (between 1 and 102 months).

29 cases (67.44%) of expired patients and 26 cases (45.61%) of live patients had pulmonary hypertension (PH). Chi square test showed that there is a significant difference (*P*: 0.04).

Signs had been improved In 25 patients (50%) of surgical group, 10 patients (55.5%) of non-surgical (Medical therapy) group and one patient (3.1%) of refusing surgery group. Chi-Square test shows that there is a significant difference between refusing surgery group and others group (*P*=.003) but no significant difference between surgery and medical groups.

Table 1. Reasons for referral among study population

Reasons for referral	N
Murmur	49
Down phenotype	19
Cyanosis	12
Tachycardia	11
Tachypnea	9

Table 2. Pattern of CHD among studied population

Type of CHD*	N
AVSD	36
VSD	35
PDA	33
ASD	22
TOF	9
COA	3
Sub Aortic Web	1

**One patient may have more than one type of lesion.*

The PAP decreased in 68.4 percent of patients with surgical therapy and 16.6 percent of patients with non-surgical (Medical therapy) therapy. PAP was not decreased in the group that refused surgery. There is a significant correlation between the type of therapy and PAP after treatment (*P*=.001).

Growth chart from the population study is shown in Fig. 1 and Fig. 2.

Table 3. Pattern of CHD based on treatment modality'*

Kind of CHD	Type of therapy		Refusing surgery (N%)	*P*-value
	Surgical (N%)	Nonsurgical (N%)		
AVSD	21(42.0)	0(0.0)	15(30.0)	0. 0
VSD	18(36.0)	7(14.0)	10(20.0)	.834
TOF	4(8.0)	0(0.0)	5(10.0)	1
PDA	19(38.0)	6(12.0)	8(16.0)	.227
ASD	11(22.0)	9(18.0)	2(4.0)	1
PS	2(4.0)	0(0.0)	0(0.0)	.495
COA	1(2.0)	0(0.0)	2(4.0)	1
Sub Aortic Web	0(0.0)	1(2.0)	0(0.0)	1

**One patient may have more than one type of lesion*

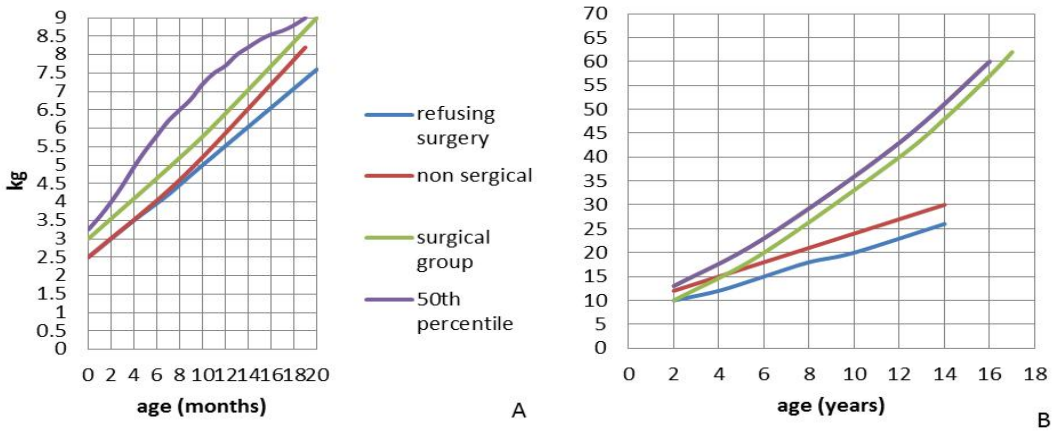

Fig. 1. Growth chart for boys of study A: Birth to 2 years old B: From 2 years to 18 years old

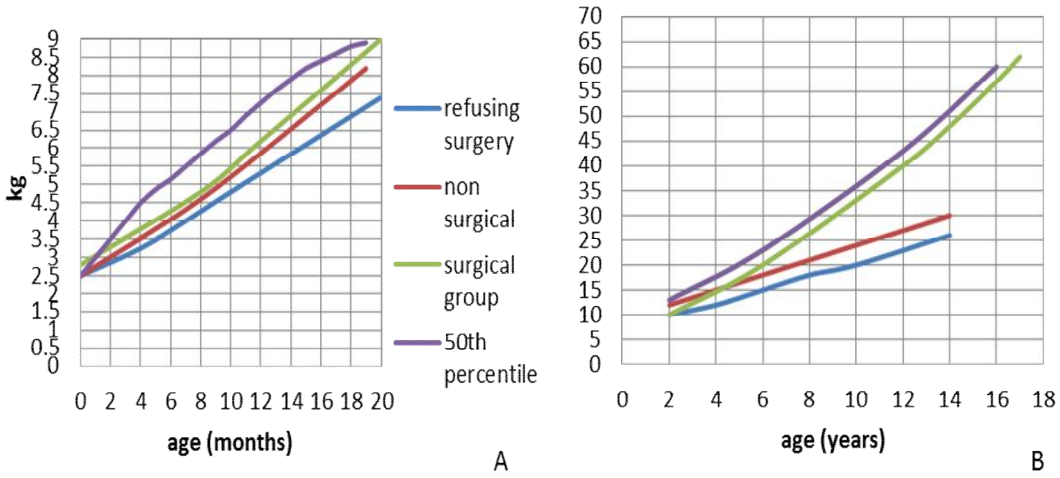

Fig. 2. Growth chart for girls of study A: Birth to 2 years old; B: From 2 years to 18 years old

The mean of birth weight in all groups were between 25th-50th percentiles. The percentile of weight after treatment was better in surgical group but it is not statically significant (*P*: 0.057). In surgical group the mean birth weight of expired patients was 2650 gr and in live patients was 2720 gr. Birth weight not influenced surgery outcome in this study.

21 patients (42%) were expired in the surgical group. 10 of them expired early after surgery. Also 3 cases (16.66%) of non-surgical group and 19 cases (59.37%) of refusing surgery group expired during follow up. The differences between refusing surgery group with two other groups are statically significant (*P*: 0.02), but there is no significant difference between surgical and non-surgical groups.

The mean age of death in the surgical group was 23 months (from 6 to 60 months) and in refusing surgery group was 7 months (from 1 to13 months). This is statically significant (Chi square *P*: 0.002).

The mean age of death in non-surgical group was 11.3 months. The common CHDs in expired patients of surgical group were AVSD (14 patients), VSD (4 patients), TOF (2 patients) and ASD (1 patient). These rates were 11 for AVSD, 4 for VSD, 3 for TOF and 1 for COA in refusing surgery group respectively. 3 cases that expired in non-surgical group had a VSD and pulmonary hypertension. These differences were not significant. (*P*: 0.61).

Among 10 patients of surgical group who expired in hospital, 7 patients had AVSD (70%) and this rate was 63.63% for patients who expired out of hospital (7 of 11 patients). Also 8 cases of in hospital mortality and 7 cases of out of hospital mortality had PH (80% compared with 63.33%)

Complications of CHD were detected in 8 patients of the surgical group (27.58% of live patients), 5 patients of non-surgical group (33.33%) and in 12 cases of refusing surgery group (92.3%).

The complications in the surgical group included residual defect in 5 patients, Pneumothorax in 1, chylothorax in 1 and AV block in 1 patient respectively.

Complications in non-surgical group included 1 AV block and 2 failures to thrive (FTT) and in refusing surgery group included FTT and Eisenmenger's Syndrome.

Complications of CHD in live patients have not significant difference in surgical compared with non-surgical (Medical Treatment) groups (Chi square *P*: 0.7) but there is statically significance between refusing group and other groups (Chi square *P*: 0.02)

In the one step surgery group 11(78.5%) patient cured, one (7.2%) cause endures complication and the other 2(14.3%) died. In the 2 step surgery group 2 patients (33.3%) were cured and the other 4(66.6%) died. These differences weren't significant, according to chi-square test. (*P*: 0.061)

Patients ran into 2 categories for echocardiography findings: Patients with any degree of CHF and patients without CHF. Among 28 patients with CHF 19 of them (67.8%) died, 3 of them (10.7%) were cured and the other 6(21.5%) ended up with complications. These rates among 72 patients without CHF were 21(29.1%), 25(34.7%) and 26(36.2%), respectively. This difference was statistically significant, according to chi-square test. (*P*: 0.02)

4. DISCUSSION

Male/Female ratio was roughly one (48%/52%) and there was no significant relationship between sex and CHD prevalence among patients which is consistent with other studies [11-13]. The mean birth weight was 2744.88 gr which was in the normal range. 70% of the patients had a birth weight in the range of 2500 to 3500 gr and about 28% of them were small for gestational age. In generalpopulation 10% of newborn had a birth weight less than 2500 gr. This difference could be caused by developmental delay in fetal period in patients with DS. Only 2% of patients were large for gestational age, which is less than the general population [14]. The mean age of diagnosis of CHD in our patients was 3.1 months and the mean age of referring to pediatric cardiologist was 5.4 months. Also the mean age of palliative surgery and corrective surgery were 12.6 and 37.2 months, respectively. There is a delay between the diagnosis age and time of surgery which the main cause was the poor compliance of parents for surgery.

In our series, specific clinical sign (murmur) was detected only in 49% of patients with CHD, and 19% had not any sign or symptom of heart disease. Others had nonspecific sign such as tachycardia, tachypnea and cyanosis, which are not specific for heart disease. So evaluation by a pediatric cardiologist and echocardiography is needed for all patients with DS, as soon as possible, and follow up evaluation and echocardiography is recommended at least up to adolescent age even in those with normal echocardiography at the first visit [15].

DS has been associated with various CHDs such as AVSD, VSD, ASD, TOF and other CHDs. In several studies, prevalence of CHD and type of CHD was variable, but in almost of them the prevalence of CHD was about 50% and the most common defects were AVSD and then VSD. In Akbari et al. [6] study in Iran AVSD (50%), VSD (21.8%), ASD (18.7%) and TOF (6.2%) were the most common type of CHDs.

In Efrén Martínez et al. [7] study AVSD was the most frequent CHD (63%) followed by VSD (26%), and eisenmenger was detected in 21% of cases. In this population study AVSD and then VSD were the most frequent CHDs, and PDA was significantly more frequent in this study than other study (33%) [6,7]. Though in our study PDA was almost always associated with other types of CHD and the isolated PDA was rarely observed. In this study, higher prevalence of PDA might relate to DS or not. So more evaluation is needed about this issue.

Some cardiac defects do not cause any problems or resolve spontaneously. Other types of defects require surgical repair. Even babies with significant defects may have no signs or symptoms. So echocardiographic evaluation is needed for these patients.

82 patients (82%) were candidate for cardiac surgery, but only 50(60.1%) of them were referred for surgery and others refused surgery (by their families). Also among 36 patients who were referred for palliative surgery only 16.6% of them had undergone for second surgery. This may be caused by economic and cultural problems. It seems education of parents and creation of inexpensive medical services is useful for these patients. Investigation of causes for refusing from treatment needs more comprehensive studies.

Finally, 50% of our patients underwent surgery while others received nonsurgical treatments. The distribution of cardiac surgical procedures performed for children with DS that was found in our study is similar to that reported by others, with AVSD repair and VSD repair being the most common procedures [9].

The clinical cure rates in surgical and refused surgery groups were amounted 50% and 3.1% respectively which the difference was noticeable. (P: 0.03).

Clinical condition and weight gain were more improved in the surgical and non-surgical groups as compared with refused surgery group. Birth weight wasn't significantly different between the groups. 12 to 24 months after getting the treatment weight percentile found to be more favorable in the surgical group than the nonsurgical one (25 to 50% and 25%, respectively), although these differences weren't statistically significant (P: 0.057).

PAP was more decreased in the surgical group and wasn't improved in neither of refusing surgery group.

Nonsurgical treatments found to be associated with more complications than surgical modalities. These differences mentioned above are statistically significant. The mortality rate was significantly different between refusing surgery compared with other groups. Also death age in the surgical group was higher than the nonsurgical group.

In our series in hospital mortality of patients who underwent surgery was 20% and made up 47.6% of all mortalities of surgical group. Most of the studies have shown no differences in postoperative mortality between DS patients and normal ones and even less postoperative mortality among DS cases [16].

Mathew et al. [17] study which is the most similar study to our series showed mortality rates 23.5% in surgical group and 76.19% in nonsurgical groups respectively. 3 out of the 4 death cases (75%) in the surgical group were caused by surgical complications which was supportive of our results. The major causes of mortality in Mathew study in nonsurgical group were CHF, pneumonia and pulmonary vascular disease respectively. The results of this study showed a more favorable improvement of patients condition in the surgical group during follow up. Issues mentioned above were supportive of our results. AL-Hayet et al. [16] study reported 30 days postoperative mortality 15%, while in Roussot et al. [18] study 30 days after AVSD surgery mortality rates were 4.9% and 5.6% in DS and normal patients respectively.

In our study, mortality was less than Mathews study, but in hospital mortalities was higher. We had a 43% mortality, but the mortality of surgical group was significantly higher (42% compared to 23.5%).

The fairly high in hospital mortality rate in the surgical group seems to be because of the high incidence of pulmonary hypertension and delay in surgery time. Mean age of operation was higher in our study (mean age for Palliative surgery and Corrective surgery operations were 12.6 months and 37.2 months, respectively).

In Rizzoli et al. [19] study 14.5% of patients died preoperatively and 5.5% of other patients died during the 15-year follow-up. The actuarial long term survival was 57% in patients with DS.

Surgery mortality in these patients has a wide range, but most of the studies suggest that if the surgery be performed on time DS will not rise the risk of mortality. Roussot et al. study suggested that the best time for the surgery is before the age of one year [18].

In Seybold et al. study Operative mortality was 41% for PAB, and 21% for aortopulmonary anastomosis. Division of a PDA hadn't any mortality. In the group of corrective cardiac surgery the operative mortality rate was 0% in ostiumprimum defects and 4% in VSD closure [20].

Many of our patients who have had palliative surgery were planned to undergo second operations, but the parents didn't follow the

advice because of the Childs death, economic limitations and poor compliance of parents.

This shows that one step surgery might be more proper for our patients because of postoperative complications and other reasons mentioned above for not attending for the second surgery. Though, complementary studies on larger sample sizes are needed for more confident conclusions.

The outcome of the disease was significantly more worsen in patients who had CHF in the first place in comparison with those who did not. These patients showed a significantly higher mortality and lower cure rates.

Besides, the outcomes of the treatment in the nonsurgical group were significantly different between those who didn't endure the surgery planned for them and those who were programmed to have the nonsurgical modalities in the first place, like the first group had one cured case, 19 death cases (59.3%) and 12 cases who ended up with complications, while these rates were 12(66.7%), 3(16.65%) and 3(16.65%) in the second group respectively.

In more of studies, surgical treatment of CHDs significantly improved clinical course and reduced mortality of the patients and more authors suggested that surgical therapy should do at an early stage of life.

According to the most studies, it is suggested that for the rapid progression of pulmonary vascular disease, operation should be performed in the first 6 months after birth. So it is considered that high PAP and age of operation are the most important causes of higher mortality rates among the surgical group in our study.

Although this research was carefully prepared, we are still aware of its limits. There was no chance for accurate study and investigation of patients suffering from other non-cardiac anomalies, because of the lack of a suitable registry system.

5. CONCLUSION

The above-mentioned diseases were not diagnosed on time and the patients underwent surgery late. Most of the patients required corrective surgery, but more of the surgeries were *palliative* surgery with more significant side effects. Finally, about half the patients expired and most of the patients had not an acceptable outcome. The most important factors in mortality in this study were CHF and PH. These patients had not good and suitable follow-up caused by several causes. So the early diagnosis of CHF is critical in this group.

CONSENT

An informed consent was taken from participants in this study.

ETHICAL APPROVAL

This Study was approved by the ethical committee of Mashhad University of Medical Sciences.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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