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# Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy

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**Abstract**

*Background:* Abnormalities in thyroid function are frequent in patients with heart failure and are associated with increased mortality. However, the relation between thyroid hormone levels and echocardiographic parameters has not been investigated sufficiently. *Aim:* The aims of this study were to investigate the correlations of thyroid hormone levels with echocardiographic parameters and to evaluate their associations with subsequent mortality in a group of patients with dilated cardiomyopathy (DCMP). *Methods:* Serum levels of thyroid hormones were measured in 111 consecutive patients with DCMP (35 female, 76 male, mean age: 62 ± 12 years). All patients underwent echocardiographic examination and were followed-up for a period of 12 ± 8 months. *Results:* Twenty-three patients (21%) had abnormalities in thyroid function tests. Free triiodothyronine (fT3)/free thyroxine (fT4) ratio was significantly correlated with most of echocardiographic parameters, such as chamber diameters and ejection fraction. Sixteen patients (14%) died during the follow-up period; their fT3/fT4 ratio was significantly lower than the patients who survived (1.31 ± 0.37 vs. 2.01 ± 0.72, $p < 0.001$). A fT3/fT4 ratio of ≤1.7 was associated with an increased risk of mortality ($p < 0.001$), independent of other prognostic markers. Sensitivity, specificity, positive and negative predictivity of fT3/fT4 ratio ≤1.7 for cardiac mortality were 100%, 71%, 36% and 100%, respectively. *Conclusion:* Determination of FT3/FT4 ratio may be a valuable and simple predictor for identification of patients with DCMP who are at high risk of subsequent mortality.


*Keywords:* Dilated cardiomyopathy; Thyroid hormones; Echocardiography; Mortality

## 1. Introduction

The changes in thyroid function that occur in almost all illnesses and after surgical procedures are defined as euthyroid sick syndrome [1,2]. Patients have normal, reduced or elevated free and total thyroxin (T4), reduced free and total triiodothyronine (T3), elevated reverse T3 and normal thyroid stimulating hormone (TSH) levels. The degree of thyroid function disturbance correlates with disease severity and low levels of thyroid hormones predict a poor prognosis in several illnesses [3].

Congestive heart failure occurs when the heart fails to provide adequate cardiac output to meet the metabolic requirements [4]. It is a hypercatabolic condition resembling chronic starvation and results in peripheral metabolic changes [5]. Patients with congestive heart failure frequently have euthyroid sick syndrome, with low T3, elevated reverse T3 and normal TSH concentrations [6,7]. Reduced T3 is associated with poor hemodynamics and a low serum sodium level, and is also an independent predictor of poor survival [8]. Several studies have investigated the value of thyroid function tests for predicting survival in congestive heart failure patients [8–10]. However, their relations to echocardiographic parameters and to general metabolic status (haematological and inflammatory markers) of the patients have not been investigated sufficiently. In this study, we measured thyroid hormone levels in a group of patients with dilated cardiomyopathy (DCMP), investigated their correlations to echocardiographic, some haematological and inflammatory parameters and evaluated their associations with subsequent mortality.

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## 2. Methods

### 2.1. Patients

The study group consisted of 111 consecutive patients (76 male, 35 female, mean age 62 ± 12 years) with the diagnosis of ischemic and non-ischemic DCMP, who had been admitted to the cardiology clinic for evaluation and treatment of congestive heart failure. Diagnosis of DCMP was based on the findings of large ventricle with left ventricular end-diastolic diameter >56 mm and dysfunctional left ventricle with ejection fraction <45%. All patients had a functional capacity of NYHA III to IV. The etiology of heart failure was investigated by coronary angiography and cardiac catheterisation in all patients.

Exclusion criteria were concomitant presence of any predominant severe systemic illness; coronary revascularization or other surgical procedures performed within the last 6 months before hospitalisation; overt hyper- or hypothyroidism; therapy with amiodarone, thyroid hormone or derivatives, dopamine, steroids or heparin; and patients who had received radiographic contrast medium within 2 weeks before measurement of thyroid hormone levels.

Thirty age and gender matched healthy volunteers recruited from a health screening programme for university personnel (18 male, 12 female, mean age: 57 ± 16) served as a control group. None of the volunteers had any concomitant disease and all physical and laboratory examination parameters were normal. The study was conducted in accordance with the Declaration of Helsinki and approved by our institutional ethics committee. All patients and controls gave informed consent prior to study entry.

### 2.2. Echocardiographic assessment

Transthoracic two-dimensional and Doppler echocardiographic assessment was performed by Toshiba SSA-390 ultrasound device using 2.5 MHz transducer. Measurements of the left atrium, left ventricle and right ventricle were obtained from parasternal long axis view and measurements of the right atrium were obtained from apical four-chamber view, according to standard criteria. Left ventricular ejection fraction was calculated using the modified Simpson's rule in the two- and four-chamber apical views. Mitral flow was evaluated from apical four-chamber view with PW-Doppler placing sample volume at the tips of mitral leaflets. Four types of diastolic filling were defined: normal filling, relaxation abnormality, pseudonormal pattern and restrictive filling.

Investigation of TEE was done by Toshiba SSA-390 echocardiography device using 7.5 MHz multiplane transducer. A topical anaesthesia was applied with 10% xylocaine, the transducer was placed in the mouth and positioned 30–40 cm away from the incisor teeth. Heart cavity images, left atrial appendage and pulmonary vein velocities were recorded with a video recorder for later review.

### 2.3. Blood samples

Fasting blood samples were drawn from a large antecubital vein of each patient for determination of biochemical and haemostatic parameters during the first 3–5 days of hospitalisation. The samples were centrifuged for 10 min and serum free-T3 (fT3), free-T4 (fT4) and TSH levels were determined by Immulite 2000 (Bio DPC, Los Angeles, USA). The reference intervals of our laboratory are as follows: TSH 0.4–4.0 mIU/ml, fT3 1.57–4.71 pg/ml and fT4 0.8–1.9 ng/dl. Hematocrit and haemoglobin levels were measured by standard methods. Plasma fibrinogen was measured by the STA Compact autoanalyser using the STA®-Fibrinogen kit.

### 2.4. Patient follow-up

Follow-up was started on the day of thyroid hormone measurements. Clinical follow-up was done by phone contact and periodical examination of patients in an outpatient clinic. All patients were followed for a mean duration of 12 ± 8 months (range 1–27 months). Endpoints of the study were cardiac death—defined as sudden death, cardiac arrest, death attributable to advanced heart failure, significant arrhythmia or new developed myocardial infarction—, cardiac transplantation and for patients with an implantable cardioverter-defibrillator device (ICD) receiving shock due to ventricular fibrillation.

### 2.5. Statistical methods

Statistical analysis was assessed with SPSS statistical package for Windows 9.0. Parametric values were given as mean ± standard deviation and non-parametric values were given as percentage. Thyroid function tests of the patients and control group were compared by unpaired Student's *t*-test. Echocardiographic and haematological correlations of thyroid hormones were assessed by Spearman correlation analysis. Differences between various types of diastolic filling were evaluated by one-way ANOVA.

Echocardiographic and haematological data of patients with and without study endpoints were compared by chi-square and Mann–Whitney *U*-tests. Mortality rates of patients by fT3/fT4 ratio were assessed by Breslow and Cox regression analysis controlling for other prognostic risk factors for heart failure. A *p*-value less than 0.05 was considered as statistically significant.

## 3. Results

Baseline characteristics of the patients with DCMP were shown in Table 1. Twenty-three patients (21%) had abnor-

Table 1
Baseline characteristics of the study group

| | |
|---|---|
| Gender (male/female) | 76/35 |
| Age (years) | 62 ± 12 |
| Hypertension | 59 (53%) |
| Diabetes | 33 (30%) |
| Coronary artery disease | 65 (59%) |
| Atrial fibrillation | 35 (32%) |
| Medications on admission | |
| Digitalis | 61 (55%) |
| ACE-I/ARB | 44 (40%) |
| Diuretics | 37 (33%) |
| Spironolactone | 6 (5%) |
| β-Blockers | 11 (10%) |
| Aspirin | 92 (83%) |
| Hemoglobin (g/dl) | 14 ± 3 |
| Hematocrit (%) | 40 ± 5 |
| Fibrinogen (mg/dl) | 436 ± 102 |
| Echocardiographic variables | |
| Left ventricular end-diastolic diameter (mm) | 64 ± 8 |
| Left ventricular end-systolic diameter (mm) | 53 ± 9 |
| Left atrium (mm) | 46 ± 6 |
| Right ventricle (mm) | 28 ± 5 |
| Ejection fraction (%) | 29 ± 10 |
| Fractional shortening (%) | 16 ± 9 |
| Left atrial appendage emptying fraction (cm/s) | 32 ± 17 |
| Left atrial appendage filling fraction (cm/s) | 32 ± 17 |

malities in thyroid function tests. The most frequent abnormality was euthyroid sick syndrome (nine patients, 8%) followed by isolated fT4 elevation (six patients, 5%), subclinical hyperthyroidism (five patients, 5%) and subclinical hypothyroidism (three patients, 3%). Mean thyroid hormone levels were within the normal range in study patients. However, when they were compared with an age-matched healthy control group, fT3 levels were found to be lower (2.6 ± 0.7 vs. 3.1 ± 0.7 pg/ml, $p = 0.001$), fT4 levels were higher (1.5 ± 0.6 vs. 1.2 ± 0.3 ng/dl, $p = 0.006$) and fT3/fT4 ratio was lower ($1.9 \pm 0.7 \times 10^{-1}$ vs. $2.7 \pm 0.8 \times 10^{-1}$, $p < 0.001$) in patients with DCMP. No difference was detected between study and control groups in terms of TSH levels (1.4 ± 1.1 vs. 1.1 ± 0.6 mIU/ml, $p$ = not significant).

### 3.1. Thyroid hormones and echocardiographic parameters

Echocardiographic correlates of thyroid hormone levels are shown in Table 2. Left atrial diameter, right heart chambers, mitral early flow velocity and severity of mitral regurgitation showed significant negative correlations with fT3 and fT3/fT4 ratio; whereas, ejection fraction, fractional shortening, deceleration time and isovolumetric relaxation time were positively correlated with these parameters.

When we assessed thyroid hormone levels according to various types of diastolic abnormality, marked differences were noted for fT3, fT4 and fT3/fT4 ratio for patients with relaxation abnormality, pseudonormal filling and restrictive filling ($p = 0.07$, $p = 0.02$ and $p < 0.001$). Particularly, fT3/fT4 ratio was significantly lower in patients with restrictive type of diastolic filling (Fig. 1).

Table 2
Echocardiographic correlates of free-T3 and free-T3/free-T4 ratio

| | Free-T3 | Free-T3/Free-T4 ratio |
|---|---|---|
| Left atrial diameter | r = – 0.20; p = 0.05 | r = – 0.27; p = 0.009 |
| Right ventricular diameter | r = – 0.24; p = 0.03 | r = – 0.27; p = 0.02 |
| Right atrial diameter | r = – 0.51; p < 0.001 | r = – 0.43; p = 0.004 |
| Ejection fraction | r = 0.11; p = NS | r = 0.20; p = 0.05 |
| Fractional shortening | r = 0.17; p = 0.09 | r = 0.29; p = 0.004 |
| Mitral early flow velocity | r = – 0.13; p = NS | r = – 0.27; p = 0.02 |
| Isovolumetric relaxation time | r = 0.25; p = 0.05 | r = 0.33; p = 0.009 |
| Deceleration time | r = 0.30; p = 0.009 | r = 0.34; p = 0.003 |
| Mitral regurgitation | r = – 0.13; p = NS | r = – 0.23; p = 0.03 |
| Left atrial appendage emptying velocity | r = 0.25; p = 0.05 | r = 0.39; p = 0.002 |
| Left atrial appendage filling velocity | r = 0.13; p = NS | r = 0.25; p = 0.05 |
| Pulmonary vein systolic flow | r = 0.08; p = NS | r = – 0.23; p = 0.03 |

Other significant correlations were detected in left atrial appendage velocities, and pulmonary vein systolic flow. Left atrial appendage emptying and filling velocities were positively correlated to fT3/fT4 ratio and negatively correlated to fT4 levels (emptying velocity: $r = -0.27$, $p = 0.04$; filling velocity: $r = -0.23$, $p = 0.07$). TSH levels were not related with any echocardiographic parameters, and except for left atrial appendage velocities, fT4 levels were also not correlated with most of the other variables.

### 3.2. Thyroid hormones and haematological parameters

There was a moderate positive correlation between hemoglobin ($r = 0.44$, $p < 0.001$), hematocrit ($r = 0.41$, $p < 0.001$)

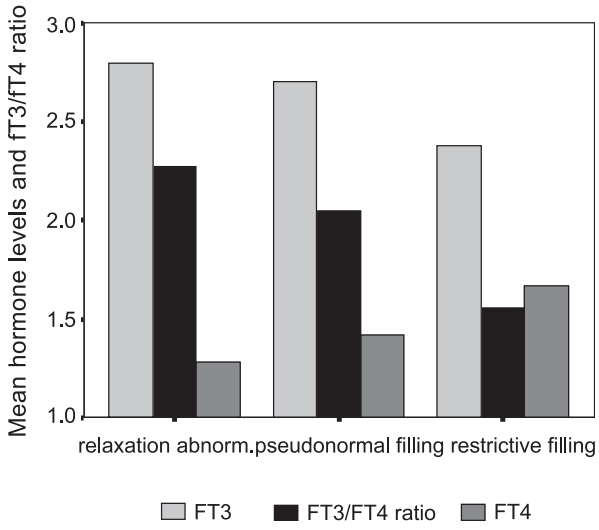


Fig. 1. Free-T3, free-T4 and free-T3/free-T4 ratio by diastolic filling type.

and fT3/fT4 ratio. Erythrocyte sedimentation rate and C-reactive protein levels were negatively correlated with fT3 levels and fT3/fT4 ratio (ESR: $r=-0.32$, $p=0.05$ and $r=-0.36$, $p=0.003$; C-reactive protein: $r=-0.25$, $p=0.05$ and $r=-0.28$, $p=0.03$, respectively). No correlation was observed between fibrinogen levels and thyroid hormones.

### 3.3. Clinical outcome

No patient died during the initial hospitalisation. Study endpoints occurred in 16 patients (14%). Fifteen patients died due to cardiac causes and one patient with ICD received shock treatment due to documented ventricular fibrillation. Eight of the deaths were due to pump failure and the other seven were either sudden death or due to documented ventricular tachyarrhythmia. When patients who died and those who survived were compared, no statistically significant difference was noted regarding age, gender, risk factors, the presence of coronary artery disease and drugs prescribed after hospitalisation.

In patients with study endpoints, diameters of right ventricle and left atrium were larger (right ventricle: $31\pm5$ vs. $27\pm5$ mm, $p=0.002$; left atrium: $49\pm6$ vs. $45\pm6$ mm, $p=0.04$), ejection fraction, fractional shortening, left atrial appendage emptying and filling velocities were lower (ejection fraction: 25% vs. 29%, $p=0.07$; fractional shortening: 13% vs. 17%, $p=0.05$; left atrial appendage emptying velocity: $24\pm14$ vs. $33\pm17$, $p=0.02$; left atrial appendage filling velocity: $24\pm16$ vs. $34\pm16$, $p=0.05$), frequency of restrictive filling pattern was higher (69% vs. 37%, $p=0.02$) and severity of mitral regurgitation was greater ($2.6\pm0.7$ vs. $2.0\pm0.8$, $p=0.02$). Hemoglobin level, hematocrit ratio, erythrocyte sedimentation rate and fibrinogen levels also showed marked differences between these two groups of patients (hemoglobin: $13\pm1.3$ vs. $14\pm3$ g/dl, $p=0.05$; hematocrit: $38\pm4$% vs. $40\pm5$%, $p=0.08$; erythrocyte sedimentation rate: $32\pm25$ vs. $20\pm18$ mm/h, $p=0.03$; fibrinogen: $486\pm85$ vs. $425\pm102$ mg/dl, $p=0.04$).

In thyroid function tests, the fT3/fT4 ratio was significantly lower in DCMP patients with study endpoints (Table 3). The highest fT3/fT4 ratio in this group was 1.67 (range 0.42–1.67), whereas in patients who survived, the maximum ratio was 3.94 (range 0.57–3.94). Survival analysis revealed a significantly less favourable outcome for patients with a fT3/fT4 ratio $\leq 1.7$, compared to patients with a higher ratio (Fig. 2). Sensitivity, specificity, positive and negative predictivity of fT3/fT4 ratio $\leq 1.7$ for study endpoints were 100%, 71%, 36% and 100%, respectively.

Table 3
Free-T3, free-T4 and TSH levels in patients with and without study endpoints (SE)

| | Patients with SE ($n=16$) | Patients without SE ($n=95$) | $p$ |
|---|---|---|---|
| Free-T3 (pg/ml) | $2.14\pm0.78$ | $2.67\pm0.68$ | 0.02 |
| Free-T4 (ng/dl) | $1.80\pm0.78$ | $1.44\pm0.50$ | NS |
| TSH | $1.41\pm0.77$ | $1.41\pm1.4$ | NS |
| f-T3/f-T4 ratio ($10^{-1}$) | $1.31\pm0.37$ | $2.01\pm0.72$ | $<0.001$ |

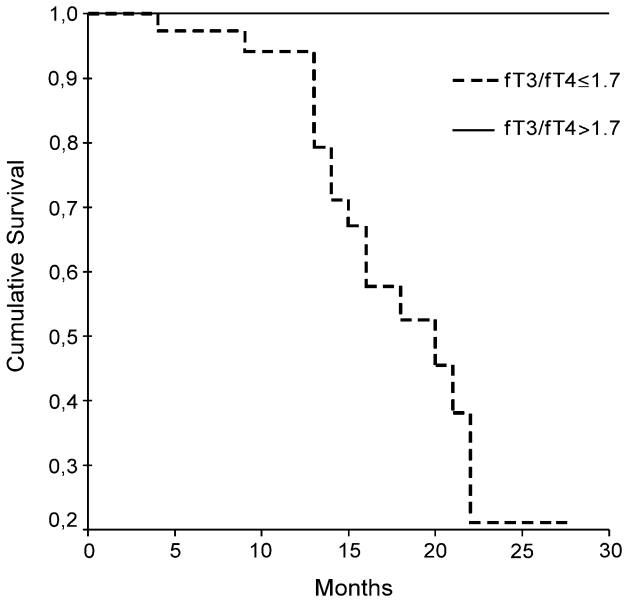


Fig. 2. Cumulative survival by free-T3/free-T4 ratio.

In Cox regression analysis adjusted for right ventricular and left atrial diameter, ejection fraction, restrictive type of diastolic filling, severity of mitral regurgitation and haemoglobin level, fT3/fT4 ratio emerged as the only significant predictor of the study endpoints ($p<0.001$). When fT3/fT4 ratio was removed from the analysis, right ventricular diameter and severe mitral regurgitation appeared as other significant correlates ($p=0.008$ and $p=0.04$, respectively).

## 4. Discussion

In this study, the alteration in thyroid hormone metabolism was a frequent finding in patients with DCMP. Euthyroid sick syndrome was the most common type of abnormality, but insignificant elevation in fT4 levels also was not rare. Low fT3 levels were associated with larger heart chambers, worse systolic and diastolic function, severe mitral regurgitation and lower flow velocities in the left atrial appendage. In order to strengthen the relation between thyroid function tests and echocardiographic parameters, the fT3 and fT4 levels were combined as fT3/fT4 ratio, which actually resulted in higher correlation coefficients and more significant $p$-values. This approach also became useful in the evaluation of subsequent mortality, because in a comparison of patients who died and those who survived the most significant difference observed was in fT3/fT4 ratio, rather than other thyroid hormone levels. In all patients with

study endpoints during the follow-up period fT3/fT4 ratio was lower than 1.7, in other words, none of the patients with fT3/fT4 ratio >1.7 died or received an ICD shock in (mean) 12 months of follow-up.

Thyroid hormone abnormalities in congestive heart failure have been reported in several previous studies with a prevalence varying between 18% and 49% [9,10]. The proportion observed in this study (21%) is similar to these previous results.

Hemodynamic correlates of low fT3 have mainly been investigated in catheterisation-based studies [8,9]. Worse hemodynamic status and low ejection fraction were clearly associated with low fT3 levels and euthyroid sick syndrome. Results of this study confirmed the previous findings about the relation of low fT3 levels to reduced ejection fraction and further showed that it is also significantly associated with enlarged heart chambers, especially right heart chambers, advanced diastolic dysfunction, lower velocities in the left atrial appendage and severe mitral regurgitation. These findings suggest that low fT3/fT4 ratio represents an advanced global impairment in heart function, or expressed another way, progressive deterioration in the left and the right ventricular and atrial function result with disturbance in thyroid hormone metabolism.

In all studies investigating prognostic value of thyroid hormones in congestive heart failure or after acute myocardial infarction, low fT3 levels, high reverse-T3 levels or presence of euthyroid sick syndrome were strong predictors for cardiac mortality and poor short term survival [8,10–12]. Only one study preferred to combine fT3 and reverse-T3 levels as fT3/r-T3 ratio [8], while the rest used one type of hormone level or just presence or absence of euthyroid sick syndrome. Friberg et al. [11] showed that reverse-T3, the inactive metabolite of T3, is positively correlated with its precursor fT4, which suggests that fT4 levels can also be used instead of r-T3. In fact, in this study fT3/fT4 ratio emerged as an independent prognostic marker for cardiac mortality and correlated with other echocardiographic signs of poor prognosis such as dilated right ventricle, restrictive filling pattern or severe mitral regurgitation.

Recent studies have shown that anaemia is a common finding in congestive heart failure. It occurs due to bone marrow suppression by cytokines and is associated with poor survival [13,14]. The positive correlation of fT3/fT4 ratio to haemoglobin levels and the negative correlation to inflammatory markers reflect a global humoral and metabolic deterioration in advanced heart failure.

Low fT3 levels in chronic illnesses and congestive heart failure occur due to reduced enzyme activity of 5′-monodeiodinase, which is responsible for converting T4 into T3 in peripheral tissues [15,16]. Liver congestion, reduced renal blood flow, poor nutritional status, peripheral metabolic changes, increase in proinflammatory cytokines, such as tumour necrosis factor alpha and interleukin-6, increased cortisol levels may all contribute to low T3 levels [8,17,18]. Although low T3 syndrome has been accepted as an adaptive process for energy consumption, it may also have deleterious effects in congestive heart failure, which can be summarized as decreased contractility and diastolic filling, increased systemic vascular resistance, diminished adrenergic activity and reduced cardiac output [19]. In an experimental study, low T3 lead to disorganisation of cultured myocardium, phenotypical remodelling of isolated cardiomyocytes and altered calcium handling, suggesting that ‘low T3 syndrome’ might influence overall myocardial architecture and contractile force [20].

### 4.1. Clinical implications

Current guidelines on diagnosis and management of heart failure recommend routine assessment of thyroid function, especially TSH levels, for detection of overt thyroid disorders, but don’t mention low T3 or euthyroid sick syndrome [21,22]. As shown in this and previous studies, TSH levels neither reflect the clinical status nor predict mortality in a majority of heart failure patients. Therefore, routine assessment of fT3 and fT4 levels and their ratio seems to be a simple and inexpensive method that provides valuable clinical information.

Treatment of low T3 levels in congestive heart failure patients had been investigated in some short-term clinical studies and in acute conditions, such as after cardiopulmonary bypass surgery or cardiogenic shock [23,24]. Although most of these studies showed beneficial effects, data about effects of long-term thyroid hormone supplementation is not yet available. The relation between heart failure and thyroid hormone changes resembles a vicious circle where impairment in heart function leads to lower T3 levels and lower T3 in turn causes decreased contractility and diastolic dysfunction. Therefore, in advanced congestive heart failure, thyroid hormone administration may help to break this vicious circle and improve the patients’ clinical status.

### 4.2. Limitations of the study

One of the limitations of the study is the lack of measurement of other laboratory prognostic markers, especially brain natriuretic peptide (BNP) level. BNP is a powerful predictor of morbidity and mortality in heart failure patients [25]. Therefore, it can be expected that BNP and fT3/fT4 may have a significant correlation.

## 5. Conclusion

In patients with DCMP, low fT3/fT4 ratio is significantly correlated with an advanced disease status and other poor prognostic markers such as reduced ejection fraction, large right ventricular diameter, severe mitral regurgitation and advanced diastolic dysfunction. Determination of fT3/fT4 ratio is a simple way to identify the high-risk and the poor outcome in these patients.

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