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ORIGINAL ARTICLE

Relationship between thyroid status and survival rates in patients presenting with acute coronary syndrome

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Thyroid dysfunction is a relatively common and treatable disease. The aims of the study included investigating the frequency of thyroid dysfunction in patients presenting with acute coronary syndrome (ACS) in our unit, following them up for 8 years and assessing the impact of thyroid dysfunction on their long-term outcome.

Thyroid dysfunction is common among patients presenting with ACS in our unit. Forty one percent (n=36) of those included had abnormal thyroid function tests at presentation with ACS, with the most common condition being subclinical hypothyroidism. The mean age of all patients was 62.3 years and there was no significant age difference between males and females. There was no significant correlation between age and TSH and age and T4 levels.

Forty two percent (n=37: 30 euthyroid, 7 thyroid dysfunction) died by the end of the observation period. A Kaplan-Meier curve was performed to check for any differences in survival across thyroid dysfunction categories. We report shorter survival times for patients who are euthyroid at presentation with an ACS.

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Introduction

Thyroid dysfunction is relatively common, readily diagnosed and treatable. Most thyroid dysfunction is subclinical and is only diagnosed with the appropriate blood test.

There are long term effects associated with thyroid dysfunction. Overt hypothyroidism and hyperthyroidism are linked to adverse cardiovascular (CV) outcomes.[1-2] Various studies have also shown that even in subclinical hypothyroidism and subclinical hyperthyroidism there is an increase in CV morbidity and mortality.[3-7]

The reason for this association is that thyroid hormone receptors are found both in the heart and vasculature. Therefore, any changes in thyroid hormone levels will affect end organ function in these areas. The relationship of thyroid hormone with the CV system is complex and the effects are modulated in several different ways. Excess thyroid hormone effects on the heart include increased heart rate, contractility and overall risk of coronary heart disease. On the other hand thyroid hormone effects on vasculature include variation in smooth muscle tone and hence blood pressure.[8-9]

Hyperthyroidism and therefore thyroid hormone excess, is associated with a hyperdynamic circulation, an increased cardiac output, subsequent development of systolic hypertension[10] and an increased risk of coronary heart disease. Hypothyroidism and hence thyroid hormone deficiency, is associated with diastolic hypertension and impaired vascular function.[11] Thyroid hormones increase endothelial production of nitric oxide and other changes which lead to changes in endothelial function due to smooth muscle relaxation.[12] Consequently, in hypothyroidism this impaired endothelial function improves with replacement of thyroid hormone.[13-14] In addition thyroid hormones have a direct effect on lipid metabolism with hyperthyroidism associated with decreased levels of cholesterol (TC)[15] and hypothyroidism with higher low density lipoprotein cholesterol (LDL-C) levels.[16] Once thyroid hormone levels normalized, lipid profiles return to normal in both hyper- and hypothyroidism. Thyroid hormones also modulate inflammatory and coagulation pathways. An overall increased hypercoagulability has been documented in hyperthyroidism,[17] while conflicting results have been reported in hypothyroidism.[18]

Overt and subclinical hyperthyroidism

Hyperthyroidism and thyroid hormone excess cause increased cardiac output by increasing stroke volume and heart rate.[19] However despite a high output state, hyperthyroid patients have reduced cardiopulmonary function during exercise due to decreased CV reserve[20]. Overt hyperthyroidism is associated with increased CV morbidity and mortality mainly due to an increased incidence of heart failure.[21-22] Untreated hyperthyroidism may cause high output heart failure even in those with a previously healthy heart. [22]

Furthermore, hyperthyroidism is associated with increased risk of atrial ectopics and atrial fibrillation. The onset of atrial fibrillation is associated with increased CV morbidity and mortality.[23] Subclinical hyperthyroidism was also shown to be associated with the development of atrial fibrillation.[7] On the other hand, studies regarding the association of CV morbidity and mortality with subclinical hyperthyroidism provide conflicting data due to major differences in study design, methods and cut-offs used. Despite this, treatment of subclinical hyperthyroidism is advocated internationally especially if the patient has

other CV risk factors and a Thyroid Stimulating Hormone (TSH) suppressed to less than 0.1mIU/L. In particular the European Thyroid Association guidelines recommend treatment in those with CV risk factors and a TSH <0.1mIU/L at any age. It is also suggested that if the patient is over 65 years and has underlying CV disease or history of fractures, treatment should be considered even if TSH is only mildly suppressed (0.1-0.39 mIU/L) in an attempt to decrease risk.[24]

A well-known long term effect of both subclinical and clinical hyperthyroidism is increased bone turnover causing osteoporosis and increased risk of fractures.[1,25] As described above, treatment is recommended to improve outcomes.

Overt and subclinical hypothyroidism

Overt hypothyroidism is associated with a reduction in cardiac output, decreased heart rate and increase in peripheral vascular resistance and diastolic dysfunction.[26] There is an association of hypercholesterolemia, diastolic hypertension and reduced endothelial nitric oxide with overt hypothyroidism. Normalization of thyroid hormone levels causes reversal of these features.[27]

Subclinical hypothyroidism is known to be associated with diastolic dysfunction due to impaired ventricular relaxation.[28] Subclinical hypothyroidism was shown to be linked to an increased risk of congestive heart failure among adults with a TSH level of 7.0 mIU/L or greater.[29] The Whickam Survey cohort showed that subclinical hypothyroidism is associated with dyslipidaemia namely higher TC levels, LDL-C levels, and triglycerides (TG).[5,30] Higher TSH levels were associated with higher systolic and diastolic blood pressure.[5,31-32]

Various studies have been published showing an association between CV outcomes and subclinical hypothyroidism. The EPIC- Norfolk study found a worse cardiovascular risk factor profile.[33] However, this increased CV risk was not confirmed in all studies. Specifically subclinical hypothyroidism was not associated with increased risk for coronary heart disease,[34-35] stroke,[36] peripheral arterial disease,[29] or CV-related or total mortality.[29]

Current data on mortality is not conclusive. Subclinical hypothyroidism was shown to be associated with an increased risk of coronary heart disease and mortality in those with higher TSH levels,[29] especially in those with a TSH concentration of 10 mIU/L or greater.[34] Subclinical hypothyroidism was also shown to be linked with an increased risk for all-cause mortality and CV death.[37] On the other hand, another study has shown that subclinical hypothyroidism might be associated with a lower risk in all cause mortality.[38] More recent studies showed no association with subclinical hypothyroidism and overall death in the elderly.[39-40] However, treatment of subclinical hypothyroidism was shown not to improve either all cause mortality,[41] or CV mortality.[42]

Aim

The aims of the study included investigating the frequency of thyroid dysfunction in patients presenting with acute coronary syndrome (ACS) to the Coronary Care Unit at St Luke's Hospital, Malta between 1st February 2002 and 30th June 2003, follow-up of these patients at St. Luke's and Mater Dei hospitals until December 2010 and assessing the impact of thyroid dysfunction on patient outcomes.

METHOD

This was a prospective, case controlled study. Patients presenting with Acute Coronary

Syndrome (ACS) at St Luke's Hospital, Malta between February 2002 and June 2003 were included in the study.

Exclusion criteria included ongoing treatment for thyroid dysfunction and ongoing treatment with beta-blockers and/or amiodarone. All patients who were admitted to CCU and did not fit in the exclusion criteria were included in this study.

Data collected included anthropometric parameters at presentation; serum and plasma samples were taken within 24 hours of presentation for thyroid function tests, renal profiles, creatinine kinase, lipid profile, random blood glucose (RBG) and glycosylated haemoglobin.

Additional data captured at presentation with ACS included diabetes subtype, current glucose lowering regime at presentation and cardiovascular risk factors, namely smoking, hypertension, dyslipidaemia, and family history.

Subsequently, follow-up data was collected until December 2010. Cardiovascular complications were recorded together with readmission rates with coronary and other events, duration of hospital stay and mortality data. Information was collected both from hospital notes and death certificates.

SPSS® 22.0 was used for data analysis. Mann-Whitney U and Kruskal-Wallis tests were used to compare differences in continuous variables between thyroid categories. Chi Square test and Kruskal-Wallis tests were used to compare frequencies across thyroid categories. Spearman's correlation was used to correlate continuous variables. Kaplan Meier survival curve was used to compare survival rates across thyroid categories. Significance was defined by a two-tailed p value of < 0.05.

Classification

The classification of thyroid status was defined in Table 1 as follows:

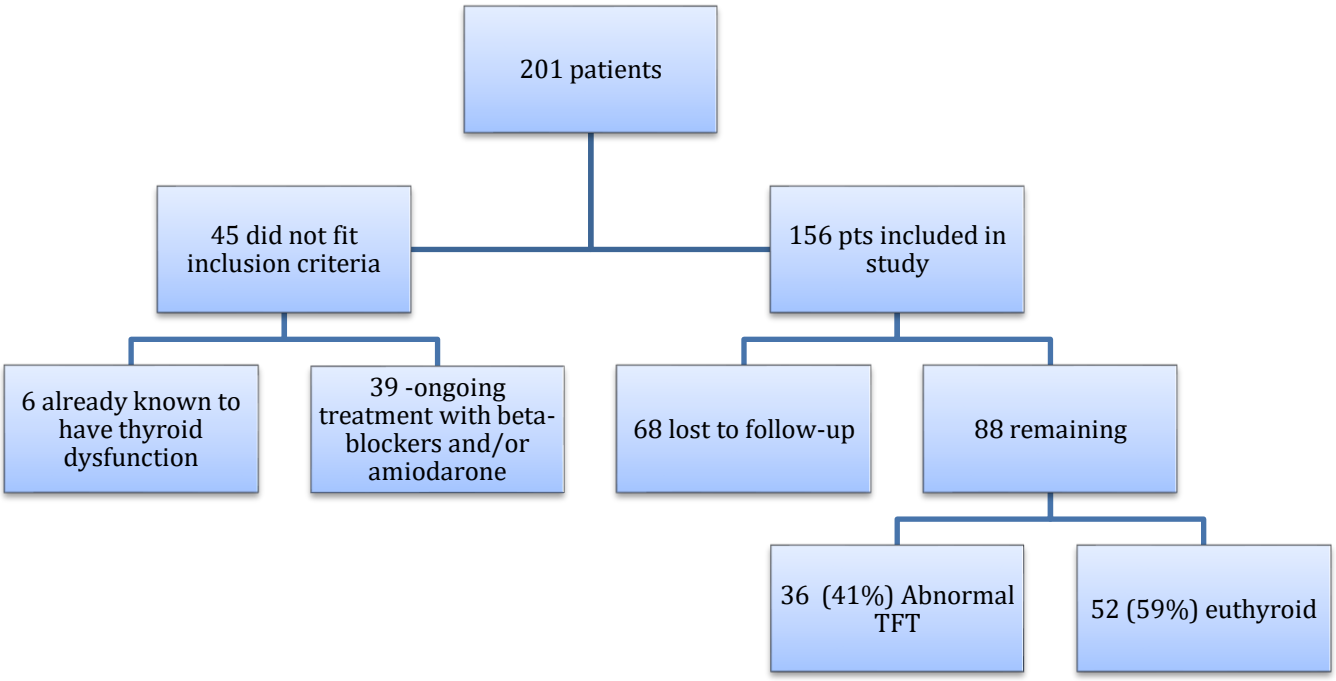
Table 1 Classification of Thyroid Status

Thyroid status	TSH and T4 concentration
Overt hypothyroidism	TSH ≥ 10 mIU/L or TSH concentration > 4.00 mIU/L with a free T4 below 10.3 pmol/l
Subclinical hypothyroidism	TSH concentration between 4 and 10 mIU/L with a normal free T4 (10.3-24.45pmol/l)
Euthyroidism	TSH concentration 0.4 to 4.0 mIU/L
Subclinical hyperthyroidism	TSH concentration > 0.1 and < 0.4 mIU/L with a normal free T4 (10.3-24.45 pmol/l)
Overt thyrotoxicosis	TSH concentration < 0.10 mU/L in the setting of a normal / elevated free T4 or a TSH value of 0.1- 0.4 in the setting of a high T4 or high T3
Sick euthyroidism	Can occur in any systemic illness and typically low FT3 and/ or FT4 with low normal/normal TSH.

RESULTS

There were a total of 201 patients admitted to the coronary care unit from February 2002 to June 2003 as shown in Figure 1. Out of these, 88 patients admitted with ACS fitted the inclusion criteria. Another 6 were admitted with ACS but were already known to have thyroid dysfunction.

Figure 1 Flow Chart of inclusion of patients



Thirty-six patients (25 males, 11 females) had abnormal thyroid function tests at presentation with ACS. Thyroid dysfunction is common among patients presenting with ACS in Malta- 41% of our cohort were newly diagnosed with thyroid dysfunction on admission. Fifty nine percent of the cohort was euthyroid at presentation. The most common thyroid dysfunction was subclinical hypothyroidism which represented 17% of the cohort followed by subclinical hyperthyroidism in 12.5% of the cohort. 9% were overtly hypothyroid and 2.2% were overtly hyperthyroid. There were no patients who met the criteria for sick euthyroid syndrome given the available thyroid hormone parameters.

The mean age of all patients was 62.3 years and there was no difference in baseline characteristics between males and females, as shown in table 2 below.

There was no definitive correlation between age and TSH and age and T4 as shown in Figure 2. Nonetheless, available data suggests a trend towards a weak correlation between TSH and age with a p value of *0.055*.

Normal thyroid and different abnormal thyroid cohorts were compared as shown in Table 3. TSH and fT4 levels were significantly different, as expected. There were no differences in age, RBG, and cholesterol across different thyroid categories.

Table 2 Baseline characteristics for all patients [Mean (SD) or frequency [%]* values]

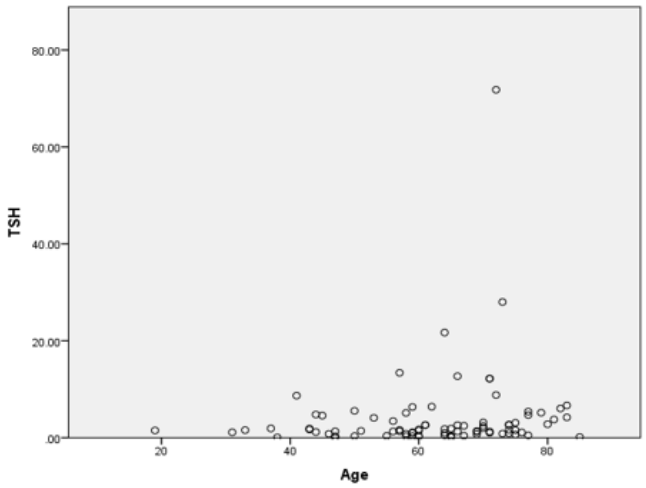
Baseline characteristic	*Males and females (N=88)*	*Males (n=52)*	*Females (n=36)*	*p value* [1]
Age (years)	62.32 (13.44)	61.94 (12.70)	62.86 (14.60)	*0.619* [2]
TSH (mIU/L)	4.08 (8.74)	4.70 (10.65)	3.16 (4.75)	*0.515* [2]
FT4 (pmol/L)	15.56 (5.00)	15.33 (4.17)	16.13 (6.79)	*0.909* [2]
Random plasma glucose (mmol/L)	9.30 (4.78)	8.76 (3.63)	10.17 (6.19)	*0.608* [2]
LDL-cholesterol (mmol/L)	3.60 (1.25)	3.62 (1.08)	3.54 (1.53)	*0.468* [2]
HDL-cholesterol (mmol/L)	1.32 (0.37)	1.28 (0.22)	1.39 (0.54)	*0.221* [2]
total cholesterol (mmol/L)	5.68 (1.48)	5.82 (1.29)	5.43 (1.80)	*0.463* [2]
suffered from diabetes at presentation*	20 (22.72)	12 (13.63)	8 (9.09)	*0.905* [3]

[1] two-sided p value for the difference between male and female subgroups

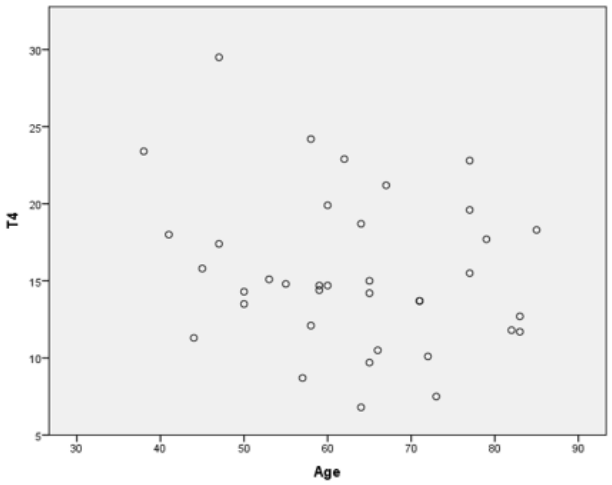
[2] Mann-Whitney U test

[3] Chi Square test

Figure 2 Correlation between age and TSH and age and T4



Spearman's rho = 0.210
p=0.055



Spearman's rho = -0.187
p=0.268

Table 3 Baseline characteristics [median values] or frequency* by thyroid category for all patients

Baseline characteristic	*Euthyroid (n= 52)*	*Overt Hypothyroid (n = 8)*	*Subclinical Hypothyroid (n=15)*	*Subclinical Hyperthyroid (n=11)*	*Overt Hyperthyroid (n=2)*	*p value* [1]
Age (years)	64	68	67	60	42.5	*0.175*
TSH (mIU/L)	1.5	13.05	5.48	0.30	0.05	*0.000*
Ft4 (pmol/L)	19.15	10.5	15.10	14.70	26.45	*0.003*
Random plasma glucose (mmol/L)	7.95	6.6	7.6	7.6	7.37	*0.281*
LDL-cholesterol (mmol/L)	3.41	4.17	3.31	2.96	2.18	*0.80*
HDL-cholesterol (mmol/L)	1.32	1.27	1.32	1.17	1.01	*0.144*
Total cholesterol (mmol/L)	5.66	6.21	5.85	5.19	3.94	*0.102*
suffered from diabetes at presentation*	13	1	6	0	0	*0.217*

[1] Independent Samples Kruskal-Wallis test

Figure 3 shows thyroid status at presentation: 52 patients were euthyroid, 8 were hypothyroid, 15 were subclinically hypothyroid, 2 were hyperthyroid and 11 were subclinically hyperthyroid.

There was no difference in counts of thyroid categories across the genders although one can say there is a trend towards some difference with a p value of *0.051 (Chi squared)*. There was also no difference in age across patients with different thyroid categories *(p=0.175- Independent Samples Kruskall Wallis test)*.

Numbers were very small. In order to perform further survival statistics, patients were divided in 2 different groups as normal thyroid function and abnormal thyroid function on admission. There was no difference in survival status between the 2 groups- *p=0.262 (Chi squared)*. As shown in Table 4.

Figure 3 Thyroid status at presentation with acute coronary syndrome

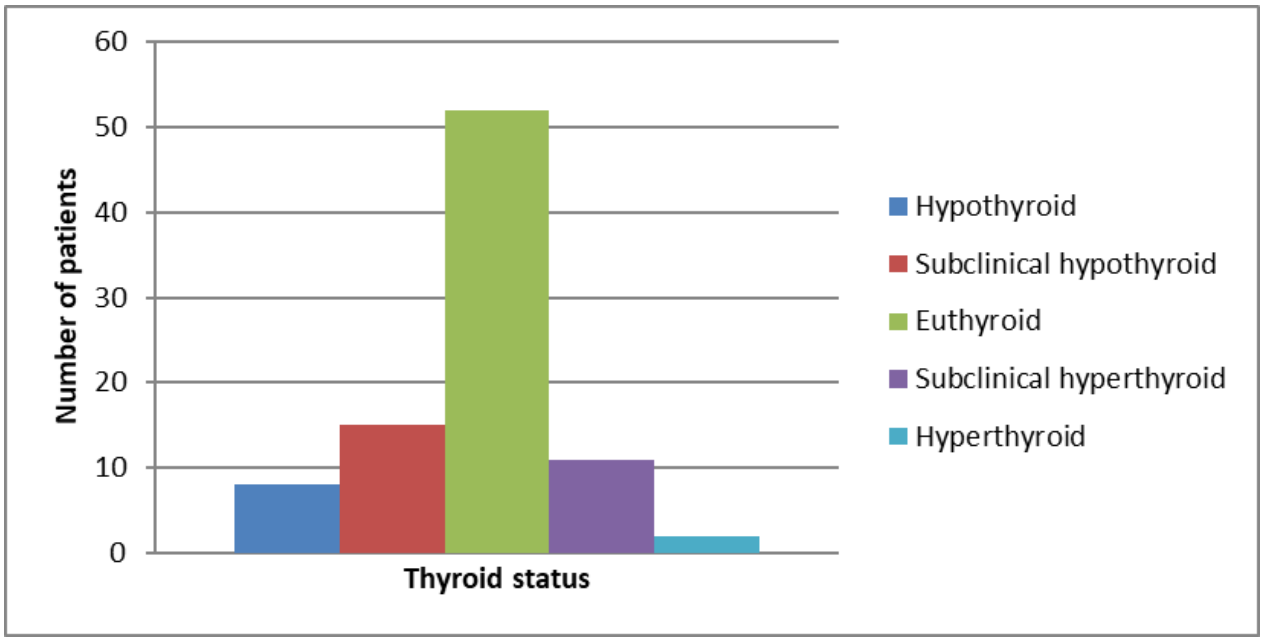


Table 4 Deaths according to thyroid status

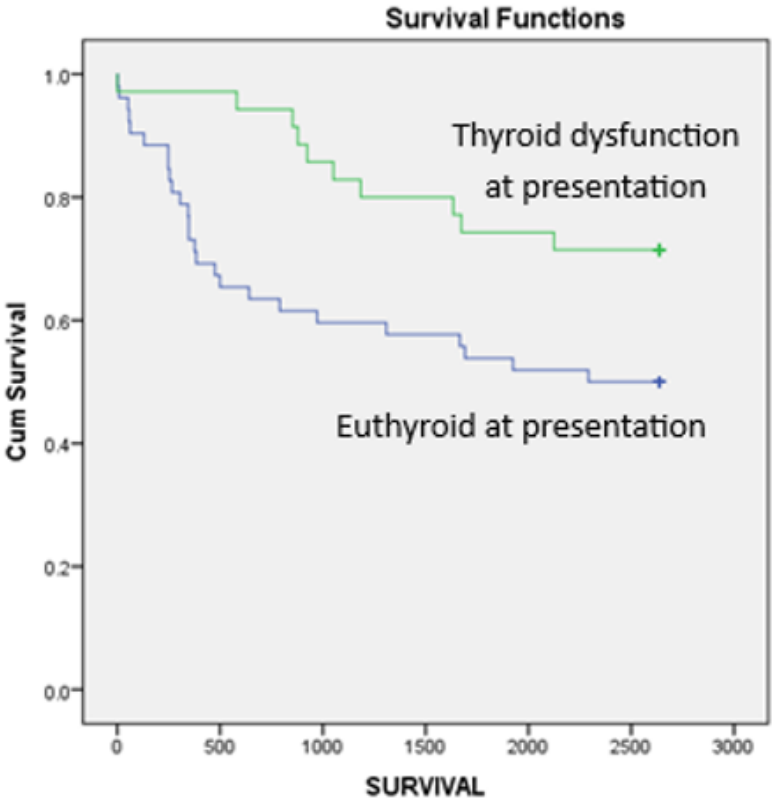
Thyroid status	Euthyroid	Abnormal thyroid function	*p value*[1]
Survived	36	15	
Died	30	7	*0.262*

Table 5 Mean survival times for patients presenting with an acute coronary syndrome, stratified by thyroid status

Thyroid status	Mean survival time	Lower 95% CI	Upper 95% CI
Euthyroid at presentation	1620.02	1318.51	1921.53
Thyroid dysfunction at presentation	2194.40	1941.77	2447.03

Kaplan-Meier curve was performed to check for any differences in survival between patients with normal and abnormal thyroid function (Log rank test with a p value of *0.191*). They were followed up for a maximum of 2636 days (Table 5 and Figure 4). By the end of the observation period in 2010, 20 male and 17 female patients had died. Causes of death stratified by thyroid status at presentation are summarised in table 6.

Figure 4 Kaplan-Meier curves comparing time to death for euthyroid patients and those with thyroid dysfunction at presentation with an acute coronary syndrome



Log-rank test p=0.027

Table 6 Causes of death across thyroid categories

Cause of death	Normal thyroid status	Thyroid dysfunction
Ischaemic/ congestive heart disease	5	2
Cerebrovascular accident	0	2
Other causes including pneumonia, sepsis	3	3
Unknown cause	18	4

Discussion

As discussed previously, the most common thyroid dysfunction was subclinical hypothyroidism (15% of the cohort) followed by 12% who were subclinical hyperthyroid. Of note, no patients were noticed to have thyroid function tests showing the sick euthyroid pattern which would be expected in a hospital cohort. Low T3 levels post myocardial infarction due to sick euthyroid syndrome have been associated with molecular changes which cause depressed myocardial function and have been implicated in the potential development of heart failure post infarction.[43] Our patients had their blood tests taken on admission, potentially prior to the occurrence of a sick euthyroid state although the lack of routine FT3 and rT3 estimations at the laboratory poses a limitation. However, T4 and TSH data did not show isolated hypothyroxinaemia.

A significant number of patients (42.05%) died during follow-up. Analysis of biochemistry results of the whole cohort on admission, revealed that twenty one percent of the cohort had been diagnosed with diabetes and a significant number had additional co-morbidities apart from coronary artery disease.

We report shorter survival times for patients who are euthyroid at presentation with an ACS, a finding that was unexpected. Most studies in the field have shown the opposite.[44-45] An explanation for this result could be the small numbers involved. Another reason could be the methodology in having grouped all thyroid dysfunction (hypothyroid and hyperthyroid) patients together in one cohort. In our cohort the euthyroid group had more diabetics than the dysthyroid group. This may have masked any opposing effects of these conditions.

In our study, there were 27 euthyroid males and 25 euthyroid females and a total of 25 male patients with thyroid dysfunction and 11 female patients with thyroid dysfunction. This is unusual as thyroid dysfunction is generally more common in females than males. In addition, women with IHD have higher rates of death compared to men after myocardial infarction[46]. It is possible that females in this cohort had more comorbidities eg higher RBG in women. Therefore, it could be that our results show a reverse mortality trend due to the gender bias, i.e. more males and hence less mortality.

A possible explanation may be that patients who have thyroid dysfunction are inevitably followed up because of the thyroid dysfunction itself and hence other issues may be picked up earlier and treated accordingly improving their survival compared to euthyroid patients.

Another explanation for our results could be that having thyroid dysfunction itself might have been the reason for the patients' ACS and hence this was easily treatable, thus decreasing mortality. On the other hand, patients who were euthyroid and had ACS, probably had non-reversible or difficult to treat causes for their IHD like hereditary causes, smoking or significant co-morbidities.

Limiting Factors

The whole cohort was a convenience sample and therefore it may not represent a normal distribution. As discussed already we had very small numbers and in addition many more male patients than female patients which may have skewed the results. Follow up data collection was retrospective and 68 case notes were unavailable (Figure 1). Hence these patients were lost to follow-up and not included in the

study. This amounted to almost a third of the cohort.

Diabetes has a huge impact in the outcome of ACS treatment. Twenty percent of our cohort had diabetes at presentation and this may have influenced their outcomes (*n*=20 of which 13 where euthyroid and 7 were dysthyroid). Management of patients of ACS varies starting from PCI to conservative management. We did not collect any data about the management of the ACS since this was beyond the scope of our study. However, the outcomes of these patients definitely may have been influenced by the type of treatment for their ACS.

Another problem was the methodology used for the Kaplan Meier analysis in grouping normal thyroid function group and abnormal thyroid function group. In grouping the different thyroid categories the analysis may have been skewed. Given the findings reported here, there is clearly a need for a larger prospective, case controlled study with prospective data collection and analysis.

Conclusions

Thyroid dysfunction is common among patients presenting with ACS in Malta, the most common being subclinical hypothyroidism. We report and discuss the observed shorter survival times for patients who are euthyroid at presentation with an acute coronary syndrome.

Summary Box

What is already known about this subject:

- Current data on mortality is not conclusive.
- Overt hypothyroidism and hyperthyroidism are linked to adverse CV outcomes.
- Various studies have also shown that even in subclinical hypothyroidism and subclinical hyperthyroidism there is an increase in CV morbidity and mortality.

What are the new findings:

- Thyroid dysfunction is common among patients presenting with ACS in Malta. Diabetes was also very common in the above cohort which may be a confounding factor.
- The most common dysfunction being subclinical hypothyroidism.
- We report shorter survival times for patients who are euthyroid at presentation with an acute coronary syndrome which is in contrast to other studies.

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