ejpmr, 2023, 10(12), 68-78

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MULTIMORBIDITY AND ITS ASSOCIATED RISK FACTORS AMONG ADULTS WITH THYROID NODULES

Imad R. Musa*

[1]Royal Commission Hospital at AL Jubail Industrial City, Al Jubail, Kingdom of Saudi Arabia.

***Corresponding Author: Dr. Imad R. Musa**

Royal Commission Hospital at AL Jubail Industrial City, Al Jubail, Kingdom of Saudi Arabia.

Article Received on 28/09/2023 **Article Revised on 19/10/2023** **Article Accepted on 09/11/2023**

ABSTRACT

Background: Multimorbidity is a complex phenomenon and a growing global health challenge. Therefore, this study aimed to investigate the prevalence of multimorbidity and its associated risk factors among adults with thyroid nodules (TNs) in the eastern region of the Kingdom of Saudi Arabia (KSA). **Methods:** A retrospective study was conducted at the Royal Commission Hospital, Eastern KSA, from January 1, 2015 to December 31, 2021. Participants' sociodemographic characteristics were assessed. Multimorbidity was defined as having more than one condition, such as diabetes mellitus (DM), hypertension, obesity, hypothyroidism, hyperthyroidism, anaemia and bronchial asthma. Multivariate regression analyses were conducted to identify any potential risk factors in multimorbid patients. **Results:** 391 adult participants with TNs were recruited in this study: The median (IQR) age was 46.00 (20.0) years of age, the majority of participants were females (84.9%) and the median (IQR) body mass index (BMI) was 30.27 (7.71) kg/m^2. A total of 208 adults (53.2%) had multimorbidity: 117 (29.9%), 51 (13.0%), 33 (8.4%), and 6 (1.5%) 1 (0.3%) had two, three, four, five and six morbidities, respectively. The remaining 54 (13.8%) and 129 (33.0%) patients had no morbidity and one morbidity, respectively. In a univariate analysis, increasing age, white blood cell count (WBCc), platelet, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4) and total cholesterol were positively associated with multimorbidity, whereas gender, low-density lipoprotein, high-density lipoprotein, triglyceride, 25-hydroxyvitamin D (25[OH)] D) levels and the outcome of thyroid ultrasound findings were not associated with multimorbidity. In a multivariate analysis, increasing age (adjusted odds ratio [AOR] = 1.057, 95% CI = 1.039 –1.075), elevated WBCc (AOR = 1.144, 95% CI 1.028 –1.274) and high FT3, (AOR = 0.703, 95% CI = 0.505 – 0.978) were associated with multimorbidity. **Conclusion:** Multimorbidity is a major public health problem among adults with TNs in the KSA. Increasing age, elevated WBCc and FT3 are significantly associated with multimorbidity.

KEYWORDS: Multimorbidity, hypertension, diabetes mellitus, obesity, anaemia, bronchial asthma, hypothyroidism, hyperthyroidism, thyroid nodules.

INTRODUCTION

Multimorbidity is defined as a given person having two or more coexisting long-term medical conditions, whether these are related or not.[1] Its prevalence has been reported to have a remarkable increase worldwide and is expected to double by 2035, particularly among individuals above 65 years with four or more chronic medical conditions.[2] Globally, the components of metabolic syndrome (hypertension and diabetes mellitus [DM]) are identified as the common disease clusters and the main drivers of multimorbidity.[3] Moreover, age, gender, obesity, education, socioeconomic status and residential regions are known predictors influencing both the prevalence and patterns of multimorbidity.[3,4] Older patients are a vulnerable group and are prone to several chronic diseases, leading to increased morbidities and mortalities as a result of reduced physical body fitness to fight multiple diseases.[5] Multimorbidity is associated with a huge burden, including cognitive, social, sexual health, psychological distress, poor medication adherence and quality of care with financial hardships to access proper medical services for multimorbidity care.[6,7] Additionally, health systems are not appropriately equipped to provide proper integrated and coordinated care to reduce the burden of multimodbidity.[6,7] Hence, the effective evaluation of multimorbidity and the improvement of the understanding of the related health problems are cornerstones for refining and improving the multimorbidity health concept that involve patients' perspectives as well as medical education and health systems to establish an integrated health system partnerships with doctors, community health providers and patients with their families.[8]

Nevertheless, TN remains a major global health problem that is defined as an abnormal lesion within the thyroid gland tissue.[9] The prevalence of TNs has markedly

increased during the last two decades. Furthermore, TNs are especially prevalent among females: women (36.51%) versus men (23.47%).[10] The estimated overall global prevalence of TNs was 24.83%, irrespective of the diagnostic techniques adopted,[10] Globally, variations in the prevalence of TNs has been reported in different areas[11] Fortunately, enough, most TNs are benign (72.5%).[12] However, the risk of thyroid malignancy requires proper early evaluation to improve prognoses and outcome to achieve a high cure rate.[13] Moreover, adoption of robust tools for assessing TNs, such as thyroid ultrasound[14,15], sonography-guided fine needle aspiration cytology (FNAC)[15,16], scoring systems for thyroid ultrasound[16], thyroid FNAC[17] and genetic and molecular testing facilities[18], has improved the accuracy of diagnosis and the safety of the technique while lowering the rate of unnecessary FNAC or thyroid gland surgeries[16,17] Some studies have demonstrated a significant association between TNs and some chronic diseases.[14,19,20] TNs are identified as a growing medical and health problem in the KSA that is especially prevalent in females and could pose considerable malignancy risks.[12,21,22] Moreover, thyroid malignancy was ranked the third most common cancer in the KSA[23] and the second most common cancer among Saudi females after breast cancer.[24] TNs in KSA are associated with significant morbidity and mortality burden[22], in addition to the financial burden, especially for those with aggressive thyroid malignancy.[25] On the other hand, recent data from KSA demonstrated multimorbidity as a considerable health problem in different regions that deserves more attention and is currently being underestimated.[26,27] Moreover, it is associated with significant morbidity rates and a high mortality rate related to multimorbidity[28], financial burdens on the health system to cover the management[29] and direct effects on the patients, particularly in older individuals with polypharmacy.[30] Recently, one study has described a high prevalence in common chronic diseases in general, such as DM (55.4%), hypertension (49.1%), DM and hypertension co-morbidity (26.8%), obesity (22.2%), anaemia (4.7%) and bronchial asthma (8.9%), in the Saudi population.[31] Similarly, some chronic diseases were reported in patients with TNs: thyroid hyper-hypofunction, DM, hypertension and bronchial asthma.[14,32] Considering the importance of multimorbidity and TNs as growing medical problems and the lack of published data on the coexistence of both conditions in the region, the current study aimed to investigate the prevalence and associated risk factors of multimorbidity among adult patients with TNs in KSA.

Methods

A retrospective study was conducted at the Royal Commission Hospital in Al Jabail Industrial City that lasted from January 1, 2015 to December 31, 2021. The electronic medical files of adult patients (men and women) aged 18 years and older were retrieved. The study included those with documented TNs based on an ultrasound procedure that was performed in the radiology department of the hospital. Medical files with incomplete data or thyroid ultrasound reports for thyroid ultrasounds performed outside the hospital were excluded. Sociodemographic data, including each patient's age, gender, weight and height, were recorded. Common comorbidities were identified using a data collection sheet: thyroid status (euthyroid, hypo or hyperthyroidism), DM, hypertension and bronchial asthma, obesity and anaemia. Similarly, laboratory tests that were conducted during a time in which TNs were collected that evaluated the following: complete blood count (WBC, haemoglobin and platelet counts), vitamin D levels, lipid profiles (total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides) and thyroid function (TSH, FT3 and FT4). Each thyroid ultrasound procedure was performed by a radiology specialist. Then, each report was reviewed and ultimately approved by a radiology consultant. The radiological department in the hospital adopted the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) for evaluating TNs (Table 1).[33]

Table (1) (TI-RADS)
Category definitions

TI-RADS -1	Benign
TI-RADS -2	Not suspicion
TI-RADS -3	Mildly suspicion
TI-RADS -4	Moderately suspicion
TI-RADS -5	Highly suspicion

ACR TI-RA
DS: American College of Radiology Thyroid Imaging Reporting and Data System.

Definition of variables

Multimorbidity is defined as the coexistence of two or longer-term medical conditions, whether related or not, in a given person.[1]

TNs: TNs were diagnosed based on the definition of the American Thyroid Association (ATA) Guidelines for assessing TNs.[9]

Body mass index (BMI): BMI was computed as the body mass divided by the square of the body height; it was expressed in units of kg/m^2, resulting from mass in kilograms and height in meters.[34] BMI was grouped according to the World Health Organization (WHO) classification: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) or obese (≥ 30.0 kg/m^2).[34]

Anaemia: Anaemia was diagnosed based on the world health organization's definition of the disease: anaemia is considered if haemoglobin concentration of < 12 g/dl in non-pregnant women and < 13 g/dl in men.[35]

Vitamin D deficiency: Vitamin D deficiencies are identified if 25-hydroxyvitamin D (25(OH)D) levels of

< 30 ng/mL; levels equal to or above this cutoff point indicate normal levels.[36]

DM: A diagnosis of DM was considered for those who had documentations of Type 1 or Type 2 and whether they were on diet control or on glucose-lowering drugs during TN assessment.

Hypertension: Patients diagnosed with hypertension and receiving treatment during assessment of TNs were considered as having hypertension.

Bronchial asthma: This variable includes individuals diagnosed with bronchial asthma based on the documentation of their medical records.

Thyroid dysfunction: Indicates the documented diagnosis of hypothyroidism or hyperthyroidism based on thyroid function tests or treatment for thyroid dysfunction on their medical records during the assessment of TNs.

Statistical analysis

Data were entered into a computer using IBM Statistical Package for the Social Sciences® (SPSS®) for Windows, version 22.0 (SPSS Inc., New York, United States). The proportions were expressed as frequencies (%). The Shapiro–Wilk test for determining the normality of continuous data (age, BMI, vitamin D levels, thyroid function test, haematological indices and lipid profile) revealed a non-normal distribution. The non-normally distributed data were expressed as the median (interquartile range [IQR]). A univariate analysis was performed for multimorbidity as the dependent variable and sociodemographic demographic (age, sex, age, BMI, vitamin D levels, thyroid function test, haematological indices, lipid profile and thyroid ultrasound findings) as independent variables. A multivariate analysis was also performed that included all variables with $p < 0.2$ to control for confounding variables. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated as they were applied. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

391 patients with documented TNs were enrolled in the study. The median (IQR) of the age was 46.00 (20.0) years and 332 (84.9%) of them were females. The median (IQR) of BMI was 30.27 (7.71) kg/m^2, 25[OH)] D level was 14.5 (12.0) nmol/L. The median (IQR) for the thyroid function test was TSH 1.71 (2.43) mmol/L, FT4 1.12 (0.45) ng/dL FT3 2.69 (0.40) nmol/L. The median (IQR) of haemoglobin was 12.6 (1.7) gm/dl, platelet count 276.15 (95.80) 10^9/L and WBCc was at 7.01 (2.63) 10^9/L. The medians (IQR) of lipid profile, total cholesterol, low-density lipoprotein, high-density lipoprotein and triglyceride were 5.8 (3.89) mmol/L, 3.76 (0.80) mmol/L, 3.00 (1.71) mmol/L and 1.78 (1.11) mmol/L respectively (Table 2).

Table 2: General Characteristics of Patients Who Had Documented Tns In Eastern Region 2015-2021.

Variables		Median	Interquartile range
Age, years		46.00	20.0
Body mass index, kg/m^2		30.27	7.71
(25[OH)]D) levels, nmol/L		14.5	12.0
TSH, mmol/L		1.71	2.43
FT3, nmol/L		2.69	0.40
FT4, ng/dL		1.12	0.45
Total cholesterol, mmol/L		5.8	3.89
Low-density lipoprotein, mmol/L		3.76	0.8
High-density lipoprotein, mmol/L		3.00	1.71
Triglyceride, mmol/L		1.78	1.11
Haemoglobin, gm/dl.		12.60	1.7
White blood cell, 10^9/L.		7.01	2.63
Platelet, 10^9/L		276.15	95.80
		Number	Proportion
Gender	Female	332	84.9
	Male	59	15.1
Anaemia	No	239	61.1
	Yes	152	38.9
Diabetes mellitus	No	297	76.0
	Yes	94	24.0
Hypertension	No	303	77.5
	Yes	72	22.5
Bronchial asthma	No	360	92.1
	Yes	31	7.9
Obesity	No	189	48.3
	Yes	202	51.7

Thyroid status	Euthyroid	250	64.0
	Hypothyroidism	112	28.6
	Hyperthyroidism	29	7.4
Ultrasound	ACR TIRADS1	10	2.6
	ACR TIRADS2	72	18.4
	ACR TIRADS3	159	40.7
	ACR TIRADS4	142	36.3
	ACR TIRADS5	8	2

Moreover, 72 (22.5%), 94 (24.0%), 31 (7.9%), 112 (28.6%) 29 (7.4%), 152 (38.9%) and 202 (51.3%) patients were diagnosed with hypertension, DM, bronchial asthma, hypothyroidism, hyperthyroidism, anaemia and obesity, respectively. A total of 208 adults (53.2%) had multimorbidity: 117 (29.9%), 51 (13.0%), 33 (8.4%), 6 (1.5%) and 1 (0.3%) patients had two, three, four, five and six morbidities, respectively. The remaining 54 (13.8%) and 129 (33.0%) patients had no morbidity and one morbidity, respectively.

The prevalence of multimorbidity among adult patients with TNs was considerably high (53.2%). The outcome of thyroid ultrasound reports based on ACR TI-RADS are as follows: ACR TI-RADS-1(2.6%), ACR TI-RADS-2 (18.4%), ACR TI-RADS-3 (40.7), ACR TI-RADS-4 (36.3%) and ACR TI-RADS-5 (2%).

In univariate analysis, no significant associations were found between multimorbidity in adult patients with TNs and gender, low-density lipoprotein, high-density lipoprotein, triglyceride, 25-hydroxyvitamin D (25[OH)] D) levels and the outcome of thyroid ultrasound. however, there was a significant association between multimorbidity in these patients and age (AOR = 1.054, 95% CI = 1.037 –1.071), WBCc, (AOR = 0.098, 95% CI = 0.996 –1.209), Platelet, (AOR = 0.998, 95% CI = 0.996 –1.000), TSH, (AOR = 1.054, 95% CI = 0.990 –1.122), FT3, (AOR = 0.654, 95% CI = 0.482 –0.887), FT4, (AOR = 0.914, 95% CI = 0.796 –1.049) and total cholesterol, (AOR = 0.809, 95% CI = 0.730 – 0.897) (Table 3).

Table 3: Univariate analysis of the predictors associated with multimorbidiy among adult patients with TNs in eastern region, 2015-2021.

Variables		Adults with no multimorbidity (n=183)	Adults multimorbidity (n=208)	OR (95.0 %CI	P
		Median			
Age, years		42.0(20.0)	52.0 (20.5)	1.054(1.037 –1.071)	0.000
White blood cell, 10^9/L		6.6 (2.7)	7.4(2.46)	0.098(0.996 –1.209)	0.059
Platelet, 10^3/dl		276.15 (80.0)	272.28(101.05)	0.998(0.996 –1.000)	0.117
TSH, mmol/L		1.7(2.12)	1.82 (2.71)	1.054(0.990 –1.122)	0.100
FT3, nmol/L		2.69(0.36)	2.69 (0.46)	0.654(0.482 –0.887)	0.006
FT4, ng/dL		1.12 (0.49)	1.12(0.42)	0.914(0.796 –1.049)	0.199
Total cholesterol, mmol/L		7.28(3.64)	5.38(4.23)	0.809(0.730 – 0.897)	0.000
Low-density lipoprotein, mmol/L		3.76(0.34)	3.76(1.12)	0.981(0.934 –1.030)	0.439
High-density lipoprotein, mmol/L		3.00 (1.54)	3.00 (1.78)	1.005(0.985 –1.024)	0.642
Triglyceride, mmol/L		2.26 (1.04)	1.55 (1.15)	0.961(0.802 –1.153)	0.670
(25[OH)]D) levels, nmol/L		14.00(10.9)	14.6 (10.9)	1.009(0.992 –1.027)	0.297
		Number			
Gender	Female	155 (84.7)	177 (85.1)	0.970(0.557 –1.688)	0.913
	Male	28 (15.3)	31 (14.9)	Reference	
Ultrasound	ACR TIRADS1	1(0.5)	9 (4.3)	Reference	
	ACR TIRADS2	35 (19.1)	37 (17.8)	15.0(1.215–185.198)	0.035
	ACR TIRADS3	77 (42.1).	82 (39.4)	1.762(0.392–7.929)	0.460
	ACR TIRADS4	65 (35.5)	77 (37.0)	1.775(0.410–7.679)	0.443
	ACR TIRADS5	5 (2.7)	3(1.4)	1.974(0.454–8.578)	0.364

In multivariate analysis, platelet count, thyroid-stimulating hormone, free thyroxine, and total cholesterol were not significantly associated with multimorbidity obesity in patients with TNs. Age (AOR = 1.057, 95% CI = 1.039 –1.075), WBCc (AOR = 1.144, 95% CI 1.028 –1.274) and FT3 (AOR = 0.703, 95% CI = 0.505 – 0.978), were highly significantly associated with multimorbidity in adult patients with TNs (Table 4).

Table 4: Multivariate analysis of the predictors associated with multimorbidiy in patient with thyroid nodules in eastern region 2015-2021.

Variables	OR (95.0 %CI	P
Age, years	1.057 (1.039 –1.075)	0.000
White blood cell, 10^9/L	1.144 (1.028 –1.274)	0.013
Platelet, 10^3/dl	0.999 (0.996 – 1.002)	0.421
Thyroid-stimulating hormone, mmol/L	1.055 (0.985–1.130)	0.129
Free thyroxine, ng/dL	0.90 (0.773 – 1.047)	0.171
Free triiodothyronine, nmol/L	0.703(0.505 – 0.978)	0.036
Total cholesterol, mmol/L	0.926 (0.819 – 1.046)	0.217

DISCUSSION

The study featured a high prevalence (53.2%) of multimorbidity among adult patients with TNs, a figure that was considerably higher than that reported in two studies assessing multimorbidity in the general population in KSA: (5.6%)[26] and (42.7%).[30] Similarly, the obtained prevalence was comparatively higher than the overall global prevalence of multimorbidity in the general population (37.2%). The regions with the highest prevalence of multimorbidity include South America (45.7%), North America (43.1%), Europe (39.2%), Asia (35%)[37] and the Middle East (21.8%).[27] The prevalence among the general population obtained in the current study was almost similar to that reported in Ethiopia (54.8%).[4] Interestingly, notable variations in the prevalence of multimorbidity in the general population was observed in low- and middle-income countries (3.2%–90.5%)[6] and among different ages: the prevalence of multimorbidity was low to moderate (3%–23%) in younger people compared to older adults (30%–87%).[3] This considerable variation in the prevalence was explained by the underestimation of multimorbidity[27,30] to some extent due to geographic variation[26], the lack of studies that have been conducted on multimorbidity[27] and the fact that both conditions (TNs and multimorbidity) are prevalent among old individuals.[31,38,39] The higher prevalence of multimorbidity identified in this study may be in concordance with the global and national growth of both multimorbidity and TNs.[2,10,12,40] Moreover, the elements of multimorbidity assessed in this study were prevalent among adult Saudi people in a particular old-age group based on recently published data.[31] Additionally, most of the subjects recruited for the current study were females (84.9%), which is consistent with the findings of some studies showing that multimorbidity was prevalent among Saudi female[41], as was DM, obesity, hypothyroidism[42] and TNs.[12] Moreover, the differences in prevalence reported in these various studies is caused by variations in the definitions adopted for multimorbidity (some studies defined it as having at least two morbidities, whereas others held that at least three chronic medical conditions were required to consider multimorbidity)[43] or the heterogeneity in methodologies.[44]

In this study, increased age is a significant predictor for multimorbidity among adult patients with TNs. This matches similar results obtained from different studies conducted in KSA and across the globe.[10,14,19,31,38–40] Similarly, the fact that both conditions (TNs and multimorbidity) are prevalent among old people[3,31,38,39] may be explained by the notion that ageing is associated with thyroid dysfunction in particular, clinical and subclinical hypo- and hyperthyroidism, thyroid nodular diseases and thyroid malignancy.[45] Moreover, advanced age is associated with TN formation as a result of degeneration of thyroid cells, leading to fibrosis, infiltration of inflammatory cells and thyroid follicle changes.[46] Furthermore, recently published data demonstrated the coexistence of both thyroid diseases and the multimorbidity, including the elements of metabolic syndrome (DM, hypertension and dyslipidemia) in the elderly.[47,48] This was strengthened by recently published data indicating that ageing was positively and directly linked to increased prevalence of multimorbidity.[41] Furthermore, ageing is associated with complex interactions between biological, psychological, behavioural, socioeconomic and environmental factors leading to increased risk of multimorbidity.[41] Additionally, most of the factors contributing to multimorbidity appear to share the same biology pathways.[49]

The current study demonstrated a significant association between higher FT3 and multimorbidity in patients with thyroid nodular diseases. A similar significance in terms of high FT3 was documented in patients with TNs, particularly elderly patients.[14] Furthermore, the same significant association of high FT3 and metabolic syndrome or its components was observed.[50–52] This may point to a close link between genetically higher BMI and higher FT3, indicating that body-fat percentage play causal roles in enhancing high FT3 levels.[53] Moreover, high levels of FT3 might induce physiological adaptation in the elderly, as higher levels of FT3 and lower levels of FT4 were associated with lower mortality rates and increase dependence on one's family.[54] This may be explained by the association of Thr92Ala-DIO2 polymorphism and clinical syndromes of multimorbidity that include hypertension, Type 2 DM, mental disorders, lung injury, bone turnover, autoimmune thyroid disease and the polymorphism in a single nucleotide (Type 2 deiodinase [Dio2]), the enzyme responsible for the conversion of thyroxine (T4) in to triiodothyronine (T3).[55] On the other hand, high levels of FT3 may be associated with the patients with hyperthyroidism included in the study and the overexpression of sodium

iodide symporter (NIS) protein in all functioning thyroid nodules (toxic adenomas), follicular cells of toxic thyroid adenomas and in 54% of benign, nonfunctioning thyroid nodules compared with the normal surrounding tissue.[56] Moreover, the adenyl cyclase system in the plasma membrane of some hyperfunctioning nodules enhances hyperresponsiveness to TSH.[57]

The current study revealed that elevated WBCc was a significant predictor for multimorbidity in patients with TNs. This aligns with similar results obtained in old patients with comorbidities.[58–60] Moreover, WBCc is deemed a valuable marker of systemic inflammation at low costs and with high precision.[59] Interestingly, WBCc is considered a more clinically useful predictor of than serum cholesterol levels in clinical geriatric settings[59], in addition to being a significant predictor that is more positively associated with overall mortality.[61] On the other hand, among the biochemistry parameters and haematological indices, WBCc and the positive rate of eosinophil percentage were significantly elevated in individuals with thyroid nodular diseases compared to those without TNs[62] and thyroid dysfunction.[63] Furthermore, in the absence of other causes for leukocytosis, elevated WBCcs were attributed to thyroid malignancy.[64] The association with multimorbidity and elevated WBCcs has been been proposed to be directly involved in the pathogenesis of vascular diseases and has merely been considered a risk indicator of vascular damage.[65] The same is applied to the well-known relationship between elevated WBCc among patients with DM[66] and metabolic syndrome.[60] Likewise, clear evidence supports the notion that neutrophil, a subgroup of WBCc, is most strongly linked with coronary risk and predicts cardiovascular death.[67,68] There are several plausible mechanisms that explain how WBCc may increase metabolic syndrome risk, as insulin resistance is considered to be the root cause of metabolic syndrome.[69] This may point to the relationship between insulin resistance and WBCc in metabolic syndrome, which is associated with pro-inflammatory cytokine release and the activation of protein kinases that subsequently impair insulin receptor substrate and reduce the expression of glucose transporter[70], eventually negatively affecting the regulation of blood glucose uptake.[71] In addition, the association between elevated WBCc and elevated blood pressure may be linked to impaired endothelial function, leading to an inflammatory process associated with reduced antioxidant and anti-inflammatory effects, increased vascular permeability, and increased inflammatory cytokines coupled with disturpted vascular endothelium protection enhanced by the production of nitric oxide and prostacyclin.[72] In contrast, the WBCs bind to the vascular endothelium, which may cause an increase in leukocytosis in the capillaries, subsequently inducing capillary stenosis, increasing vascular pressure and eventually leading to permanent hypertension.[73] Interestingly, experimental animal data suggest that the effects of lymphocytes could be mediated by modulating vascular function, sympathetic outflow, renal sodium reabsorption and salt handling via antigen-presenting cells to develop hypertension.[74] It is relevant to note that anaemia was associated with reactive hyperleukocytosis and thrombocytosis that rapidly resolved after correction of anaemia.[75,76] Moreover WBCc was linked with bronchial asthma, particularly during the exacerbation of the disease, as it predicts the length of hospital stay and mechanical ventilation rate.[77] Moreover, the activation of Th1- and Th2-associated interferons, interleukin, specific interleukin proteins and cytokines in patients with bronchial asthma.[78] In addition, it has been suggested that neutrophils play a role in bronchial asthma pathophysiology.[79] In this study, the remaining variables showed a non-significant association between multimorbidity among adults with TNs, as reported in recently published data.[14,20,80] This may be explained by the fact that TN pathogenesis[81] and multimorbidity[82] are both of multifactorial aetiology enhanced by genetic predisposition and the individuals' environmental interactions. Hence, the mechanisms underlying the development of multimorbidity are complex, multilevel and interrelated, which should encourage additional research in the multimorbidity field and the training of medical and health staff involved in the management along with reconfiguration of health care supporting the management to improve the outcomes and prognoses for this vulnerable group of patients aligned with patients' values and safety.[82]

This study has several limitations: it is a retrospective study and was conducted in only one centre; the definition of multimorbidity is not globally unified (in this study, patients having two or more coexistent morbidities indicated multimorbidity); and certain risk factors were not assessed, such as diet, physical exercise, smoking and alcohol consumption. Moreover, detailed information regarding disease severity and income was not included due to data availability issues. The data obtained showed a comprehensive multimorbidity pattern prevalent in the elderly. Finally, certain important diseases that are more prevalent among older individuals, such as prostate diseases, osteoarthritis and cancer, were not included. This limitation may lead to an underestimation of the prevalence of multimorbidity and the misclassification of multimorbidity patterns.

CONCLUSION

The high prevalence of multimorbidity among adult patients with TNs indicates that multimorbidity is a major public health problem. Moreover, extensive studies are required to assess the magnitude of multimorbidity to improve future planning and establish effective health systems. Old age, elevated FT3 and WBCc appeared to be significant predictors for multimorbidity in this group of patients.

Abbreviations

KSA: Kingdom of Saudi Arabia; TNs: thyroid nodules.; IQR: interquartile range.; AOR: Adjusted odds ratio;

(25[OH)] D): 25-hydroxyvitamin D; TSH: Thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; WBCc: White blood cell count; DM: Diabetes mellitus; BMI: Body mass index; CI: confidence interval; SD: Standard deviation; FNAC: Thyroid fine-needle aspiration cytological; TI-RADS: Thyroid ultrasound reports based on thyroid imaging reporting and data system.

Declarations

Availability of data and material

Data are available upon request.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Royal Commission Hospital, KSA (IB-RCH-012), which waived verbal or written consent from the participants. It was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Consent for publication

Not applicable.

Conflicts of Interest

The author has no conflicts of interest to declare.

Disclosure

No funding received.

Corresponding Author

Imad R. Musa, Royal Commission Hospital at AL Jubail Industrial City, Al Lulu Road, Al Fanateer, Al Jubail 31961, Kingdom of Saudi Arabia.

ORCID iD: Imad R. Musa https://orcid.org/0000-0002-1138-0710

REFERENCES

1. Starfield, B. Challenges to Primary Care from Co- and Multi-Morbidity. *Prim. Health Care Res. Dev.*, 2011; *12:* 1–2, doi:10.1017/S1463423610000484.
2. Kingston, A.; Robinson, L.; Booth, H.; Knapp, M.; Jagger, C.; Adelaja, B.; Avendano, M.; Bamford, S.M.; Banerjee, S.; Berwald, S.; et al. Projections of Multi-Morbidity in the Older Population in England to 2035: Estimates from the Population Ageing and Care Simulation (PACSim) Model. *Age Ageing*, 2018; *47:* 374–380. doi:10.1093/AGEING/AFX201.
3. Roomaney, R.A.; van Wyk, B.; Turawa, E.B.; Pillay-van Wyk, V. Multimorbidity in South Africa: A Systematic Review of Prevalence Studies. *BMJ Open*, 2021; *11:* e048676. doi:10.1136/BMJOPEN-2021-048676.
4. Eyowas, F.A.; Schneider, M.; Balcha, S.A.; Pati, S.; Getahun, F.A. Multimorbidity and Health-Related Quality of Life among Patients Attending Chronic Outpatient Medical Care in Bahir Dar, Northwest Ethiopia: The Application of Partial Proportional Odds Model. *PLOS Glob. public Heal*, 2022; *2:* e0001176, doi:10.1371/JOURNAL.PGPH.0001176.
5. Nguyen, H.; Manolova, G.; Daskalopoulou, C.; Vitoratou, S.; Prince, M.; Prina, A.M. Prevalence of Multimorbidity in Community Settings: A Systematic Review and Meta-Analysis of Observational Studies. *J. comorbidity*, 2019; *9.* 2235042X1987093, doi:10.1177/2235042X19870934.
6. Eyowas, F.A.; Schneider, M.; Alemu, S.; Getahun, F.A. Experience of Living with Multimorbidity and Health Workers Perspectives on the Organization of Health Services for People Living with Multiple Chronic Conditions in Bahir Dar, Northwest Ethiopia: A Qualitative Study. *BMC Health Serv. Res.*, 2023; *23*. doi:10.1186/S12913-023-09250-9.
7. Prince, M.J.; Wu, F.; Guo, Y.; Gutierrez Robledo, L.M.; O'Donnell, M.; Sullivan, R.; Yusuf, S. The Burden of Disease in Older People and Implications for Health Policy and Practice. *Lancet (London, England)*, 2015; *385:* 549–562. doi:10.1016/S0140-6736(14)61347-7.
8. Roche, S.; de Vries, E. Multimorbidity in a Large District Hospital: A Descriptive Cross-Sectional Study. *S. Afr. Med. J.*, 2017; *107:* 1110–1115. doi:10.7196/SAMJ.2017.V107I12.12397.
9. Cooper, D.S.; Doherty, G.M.; Haugen, B.R.; Kloos, R.T.; Lee, S.L.; Mandel, S.J.; Mazzaferri, E.L.; McIver, B.; Pacini, F.; Schlumberger, M.; et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*, 2009; *19:* 1167–1214. doi:10.1089/THY.2009.0110.
10. Mu, C.; Ming, X.; Tian, Y.; Liu, Y.; Yao, M.; Ni, Y.; Liu, Y.; Li, Z. Mapping Global Epidemiology of Thyroid Nodules among General Population: A Systematic Review and Meta-Analysis. *Front. Oncol.*, 2022; *12*. doi:10.3389/FONC.2022.1029926.
11. Sajisevi, M.; Caulley, L.; Eskander, A.; Du, Y.; Auh, E.; Karabachev, A.; Callas, P.; Conradie, W.; Martin, L.; Pasternak, J.; et al. Evaluating the Rising Incidence of Thyroid Cancer and Thyroid Nodule Detection Modes: A Multinational, Multi-Institutional Analysis. *JAMA Otolaryngol. Head Neck Surg.*, 2022; *148.* doi:10.1001/JAMAOTO.2022.1743.
12. Alqahtani, S.M. Cytological Patterns of Thyroid Lesions in Najran, Saudi Arabia: A 5-Year Retrospective Study. *Saudi Med. J.*, 2022; *43:* 735–742. doi:10.15537/SMJ.2022.43.7.20220223.
13. Uppal, N.; Collins, R.; James, B. Thyroid Nodules: Global, Economic, and Personal Burdens. *Front. Endocrinol. (Lausanne)*, 2023; *14.* doi:10.3389/FENDO.2023.1113977.
14. Alyousif, H.; Ahmed, M.A.S.; Khair, A.M.; Alharbi, F.H.; Hassan, S.; Elbadwi, N.M.; Musa, I.R. The Prevalence and Associated Predictors for Diabetes Mellitus in Adult Patients With Thyroid Nodules. *J. Clin. Med. Res.*, 2023; *15:* 166–173. doi:10.14740/JOCMR4886.
15. Yang, X.; Zhai, D.; Zhang, T.; Zhang, S. Use of

Strain Ultrasound Elastography versus Fine-Needle Aspiration Cytology for the Differential Diagnosis of Thyroid Nodules: A Retrospective Analysis. *Clinics (Sao Paulo)*, 2020; *75:* 1–8. doi:10.6061/CLINICS/2020/E1594.
16. Al-Ghanimi, I.; Al-Sharydah, A.; Al-Mulhim, S.; Faisal, S.; Al-Abdulwahab, A.; Al-Aftan, M.; Abuhaimed, A. Diagnostic Accuracy of Ultrasonography in Classifying Thyroid Nodules Compared with Fine-Needle Aspiration. *Saudi J. Med. Med. Sci.*, 2020; *8:* 25. doi:10.4103/SJMMS.SJMMS_126_18.
17. Pandya, A.; Caoili, E.M.; Jawad-Makki, F.; Wasnik, A.P.; Shankar, P.R.; Bude, R.; Haymart, M.R.; Davenport, M.S. Retrospective Cohort Study of 1947 Thyroid Nodules: A Comparison of the 2017 American College of Radiology TI-RADS and the 2015 American Thyroid Association Classifications. *AJR. Am. J. Roentgenol.*, 2020; *214:* 900–906. doi:10.2214/AJR.19.21904.
18. Livhits, M.J.; Zhu, C.Y.; Kuo, E.J.; Nguyen, D.T.; Kim, J.; Tseng, C.H.; Leung, A.M.; Rao, J.; Levin, M.; Douek, M.L.; et al. Effectiveness of Molecular Testing Techniques for Diagnosis of Indeterminate Thyroid Nodules: A Randomized Clinical Trial. *JAMA Oncol.*, 2021; *7:* 70–77. doi:10.1001/JAMAONCOL.2020.5935.
19. Zhang, C.; Gao, X.; Han, Y.; Teng, W.; Shan, Z. Correlation Between Thyroid Nodules and Metabolic Syndrome: A Systematic Review and Meta-Analysis. *Front. Endocrinol. (Lausanne)*, 2021; *12*. doi:10.3389/FENDO.2021.730279.
20. Liu, J.; Wang, C.; Tang, X.; Fu, S.; Jing, G.; Ma, L.; Sun, W.; Li, Y.; Wu, D.; Niu, Y.; et al. Correlation Analysis of Metabolic Syndrome and Its Components with Thyroid Nodules. *Diabetes, Metab. Syndr. Obes. Targets Ther.*, 2019; *12:* 1617. doi:10.2147/DMSO.S219019.
21. Hussain, F.; Iqbal, S.; Mehmood, A.; Bazarbashi, S.; ElHassan, T.; Chaudhri, N. Incidence of Thyroid Cancer in the Kingdom of Saudi Arabia, 2000-2010. *Hematol. Oncol. Stem Cell Ther.*, 2013; *6:* 58–64. doi:10.1016/J.HEMONC.2013.05.004.
22. Flemban, A.F.; Kabrah, S.; Alahmadi, H.; Alqurashi, R.K.; Turaes, A.S.; Almaghrabi, R.; Al Harbi, S.; Khogeer, A.A. Patterns of Thyroid Cancer Mortality and Incidence in Saudi Arabia: A 30-Year Study. *Diagnostics (Basel, Switzerland)*, 2022; *12*. doi:10.3390/DIAGNOSTICS12112716.
23. Alqahtani, W.S.; Almufareh, N.A.; Domiaty, D.M.; Albasher, G.; Alduwish, M.A.; Alkhalaf, H.; Almuzzaini, B.; AL-Marshidy, S.S.; Alfraihi, R.; Elasbali, A.M.; et al. Epidemiology of Cancer in Saudi Arabia Thru 2010–2019: A Systematic Review with Constrained Meta-Analysis. *AIMS Public Heal.*, 2020; *7:* 679. doi:10.3934/PUBLICHEALTH.2020053.
24. Alshehri, B. Descriptive Epidemiological Analysis of Thyroid Cancer in theSaudi Population (2001-2013). *Asian Pac. J. Cancer Prev.*, 2017; *18:* 1445–1451. doi:10.22034/APJCP.2017.18.5.1445.
25. Nejadghaderi, S.A.; Moghaddam, S.S.; Azadnajafabad, S.; Rezaei, N.; Rezaei, N.; Tavangar, S.M.; Jamshidi, H.; Mokdad, A.H.; Naghavi, M.; Farzadfar, F.; et al. Burden of Thyroid Cancer in North Africa and Middle East 1990-2019. *Front. Oncol.*, 2022; *12*. doi:10.3389/FONC.2022.955358.
26. Algabbani, A.; Alqahtani, A.; BinDhim, N. Prevalence and Determinants of Non-Communicable Diseases in Saudi Arabia. *Food Drug Regul. Sci. J.*, 2019; *2:* 1. doi:10.32868/RSJ.V2I2.29.
27. Singh, K.; Alomari, A.; Lenjawi, B. Prevalence of Multimorbidity in the Middle East: A Systematic Review of Observational Studies. *Int. J. Environ. Res. Public Health*, 2022; *19*. doi:10.3390/IJERPH192416502.
28. Alzahrani, M.S.; Alharthi, Y.S.; Aljamal, J.K.; Alarfaj, A.A.; Vennu, V.; Noweir, M.D. National and Regional Rates of Chronic Diseases and All-Cause Mortality in Saudi Arabia-Analysis of the 2018 Household Health Survey Data. *Int. J. Environ. Res. Public Health*, 2023; *20*. doi:10.3390/IJERPH20075254.
29. Schiltz, N.K. Prevalence of Multimorbidity Combinations and Their Association with Medical Costs and Poor Health: A Population-Based Study of U.S. Adults. *Front. public Heal.*, 2022; *10*. doi:10.3389/FPUBH.2022.953886.
30. Almutairi, A.S.; Alhazmi, T.M.; Alotaibi, Y.H.; Alfraidi, A.A.; Alsaad, A.M.; Matrood, R.A.; Al-khatir, A.N.; Alsubaie, A.A.; Alotibi, W.M. Medication Adherence Among Multimorbid Patients With Polypharmacy and Its Relation to Social Support at National Guard Primary Health Care Centers, Riyadh. *Cureus*, 2022; *14:* doi:10.7759/CUREUS.30679.
31. Al-Amoud, M.M.; Omar, D.I.; Almashjary, E.N.; Alomary, S.A. Morbidity Profile among Older People at Primary Health Care Centers in Saudi Arabia during the Period 2012-2020. *Saudi Med. J.*, 2023; *44:* 45. doi:10.15537/SMJ.2023.44.1.20220465.
32. Bukasa, J.K.; Bayauli-Mwasa, P.; Mbunga, B.K.; Bangolo, A.; Kavula, W.; Mukaya, J.; Bindingija, J.; M'Buyamba-Kabangu, J.R. The Spectrum of Thyroid Nodules at Kinshasa University Hospital, Democratic Republic of Congo: A Cross-Sectional Study. *Int. J. Environ. Res. Public Health*, 2022; *19:* doi:10.3390/IJERPH192316203.
33. Tessler, F.N.; Middleton, W.D.; Grant, E.G.; Hoang, J.K.; Berland, L.L.; Teefey, S.A.; Cronan, J.J.; Beland, M.D.; Desser, T.S.; Frates, M.C.; et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. *J. Am. Coll. Radiol.*, 2017; *14:* 587–595. doi:10.1016/J.JACR.2017.01.046.
34. NHLBI Obesity Education Initiative, Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical Guidelines on the Identification, Evaluation, and Treatment of

Overweight and Obesity in Adults, 1998.
35. Domenica Cappellini, M.; Motta, I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? *Semin. Hematol*, 2015; *52:* 261–269. doi:10.1053/J.SEMINHEMATOL.2015.07.006.
36. Alzaheb, R.A. The Prevalence of Hypovitaminosis D and Its Associated Risk Factors Among Women of Reproductive Age in Saudi Arabia: A Systematic Review and Meta-Analysis. *Clin. Med. insights. Women's Heal.*, 2018; *11:* 1179562X1876788. doi:10.1177/1179562X18767884.
37. Chowdhury, S.R.; Chandra Das, D.; Sunna, T.C.; Beyene, J.; Hossain, A. Global and Regional Prevalence of Multimorbidity in the Adult Population in Community Settings: A Systematic Review and Meta-Analysis. *EClinicalMedicine*, 2023; *57*. doi:10.1016/J.ECLINM.2023.101860.
38. Patel, P.; Muhammad, T.; Sahoo, H. The Burden of Disease-Specific Multimorbidity among Older Adults in India and Its States: Evidence from LASI. *BMC Geriatr*, 2023; *23*. doi:10.1186/S12877-023-03728-1.
39. Ospina, N.S.; Papaleontiou, M. Thyroid Nodule Evaluation and Management in Older Adults: A Review of Practical Considerations for Clinical Endocrinologists. *Endocr. Pract.*, 2021; *27:* 261–268. doi:10.1016/J.EPRAC.2021.02.003.
40. Melis, R.; Marengoni, A.; Angleman, S.; Fratiglioni, L. Incidence and Predictors of Multimorbidity in the Elderly: A Population-Based Longitudinal Study. *PLoS One*, 2014; *9*. doi:10.1371/JOURNAL.PONE.0103120.
41. Kadambi, S.; Abdallah, M.; Loh, K.P. Multimorbidity, Function, and Cognition in Aging. *Clin. Geriatr. Med.*, 2020; *36:* 569–584. doi:10.1016/J.CGER.2020.06.002.
42. Ahmed, A.E.; Alsamghan, A.; Momenah, M.A.; Alqhtani, H.A.; Aldawood, N.A.; Alshehri, M.A.; Ali Alshehri, A.M.; Alhag, S.K.; Mosaad, Y.O.; Ahmed, H. Metabolic Syndrome and Cardiometabolic Risk Factors in the Mixed Hypercholesterolemic Populations with Respect to Gender, Age, and Obesity in Asir, Saudi Arabia. *Int. J. Environ. Res. Public Health*, 2022; *19*. doi:10.3390/IJERPH192214985.
43. Chua, Y.P.; Xie, Y.; Lee, P.S.S.; Lee, E.S. Definitions and Prevalence of Multimorbidity in Large Database Studies: A Scoping Review. *Int. J. Environ. Res. Public Health*, 2021; *18:* 1–12. doi:10.3390/IJERPH18041673.
44. Xu, X.; Mishra, G.D.; Jones, M. Evidence on Multimorbidity from Definition to Intervention: An Overview of Systematic Reviews. *Ageing Res. Rev.*, 2017; *37:* 53–68. doi:10.1016/J.ARR.2017.05.003.
45. Nagaratnam, N.; Nagaratnam, K.; Cheuk, G. Thyroid Disease in the Older Patient. *Geriatr. Dis.*, 2017; 1–14. doi:10.1007/978-3-319-32700-6_47-1.
46. Saad, A.G.; Kumar, S.; Ron, E.; Lubin, J.H.; Stanek, J.; Bove, K.E.; Nikiforov, Y.E. Proliferative Activity of Human Thyroid Cells in Various Age Groups and Its Correlation with the Risk of Thyroid Cancer after Radiation Exposure. *J. Clin. Endocrinol. Metab.*, 2006; *91:* 2672–2677. doi:10.1210/JC.2006-0417.
47. Li, Y.; Teng, D.; Ba, J.; Chen, B.; Du, J.; He, L.; Lai, X.; Teng, X.; Shi, X.; Li, Y.; et al. Efficacy and Safety of Long-Term Universal Salt Iodization on Thyroid Disorders: Epidemiological Evidence from 31 Provinces of Mainland China. *Thyroid*, 2020; *30:* 568–579. doi:10.1089/THY.2019.0067.
48. Zhu, Y.; Xu, F.; Shen, J.; Liu, Y.; Bi, C.; Liu, J.; Li, Y.; Wang, X.; Gao, Z.; Liang, L.; et al. Prevalence of Thyroid Dysfunction in Older Chinese Patients with Type 2 Diabetes-A Multicenter Cross-Sectional Observational Study across China. *PLoS One*, 2019; *14*. doi:10.1371/JOURNAL.PONE.0216151.
49. Barnes, P.J. Mechanisms of Development of Multimorbidity in the Elderly. *Eur. Respir. J.*, 2015; *45:* 790–806. doi:10.1183/09031936.00229714.
50. Wolffenbuttel, B.H.R.; Wouters, H.J.C.M.; Slagter, S.N.; van Waateringe, R.P.; Muller Kobold, A.C.; van Vliet-Ostaptchouk, J. V.; Links, T.P.; van der Klauw, M.M. Thyroid Function and Metabolic Syndrome in the Population-Based LifeLines Cohort Study. *BMC Endocr. Disord.*, 2017; *17*. doi:10.1186/S12902-017-0215-1.
51. Kim, H.J.; Bae, J.C.; Park, H.K.; Byun, D.W.; Suh, K.; Yoo, M.H.; Kim, J.H.; Min, Y.K.; Kim, S.W.; Chung, J.H. Triiodothyronine Levels Are Independently Associated with Metabolic Syndrome in Euthyroid Middle-Aged Subjects. *Endocrinol. Metab. (Seoul, Korea)*, 2016; *31:* 311–319. doi:10.3803/ENM.2016.31.2.311.
52. Park, S.Y.; Park, S.E.; Jung, S.W.; Jin, H.S.; Park, I.B.; Ahn, S.V.; Lee, S. Free Triiodothyronine/Free Thyroxine Ratio Rather than Thyrotropin Is More Associated with Metabolic Parameters in Healthy Euthyroid Adult Subjects. *Clin. Endocrinol. (Oxf)*, 2017; *87:* 87–96. doi:10.1111/CEN.13345.
53. Taylor, P.N.; Richmond, R.; Davies, N.; Sayers, A.; Stevenson, K.; Woltersdorf, W.; Taylor, A.; Groom, A.; Northstone, K.; Ring, S.; et al. Paradoxical Relationship Between Body Mass Index and Thyroid Hormone Levels: A Study Using Mendelian Randomization. *J. Clin. Endocrinol. Metab.*, 2016; *101:* 730–738. doi:10.1210/JC.2015-3505.
54. Van Vliet, N.A.; van der Spoel, E.; Beekman, M.; Slagboom, P.E.; Blauw, G.J.; Gussekloo, J.; Westendorp, R.G.J.; van Heemst, D. Thyroid Status and Mortality in Nonagenarians from Long-Lived Families and the General Population. *Aging (Albany. NY).*, 2017; *9:* 2220–2231. doi:10.18632/AGING.101310.
55. Bianco, A.C.; Kim, B.S. Pathophysiological Relevance of Deiodinase Polymorphism. *Curr. Opin. Endocrinol. Diabetes. Obes.*, 2018; *25:* 341–346. doi:10.1097/MED.0000000000000428.
56. Tonacchera, M.; Viacava, P.; Agretti, P.; De Marco, G.; Perri, A.; Cosmo, C. Di; De Servi, M.; Miccoli, P.; Lippi, F.; Naccarato, A.G.; et al. Benign

Nonfunctioning Thyroid Adenomas Are Characterized by a Defective Targeting to Cell Membrane or a Reduced Expression of the Sodium Iodide Symporter Protein. *J. Clin. Endocrinol. Metab*, 2002; *87:* 352–357. doi:10.1210/JCEM.87.1.8173.

57. Walinder, O.; Karlsson, F.A.; Dahlberg, P.A. Adenyl Cyclase Activity in Human Thyroid Plasma Membranes from Normal Human Thyroid Tissue and Thyroid Adenomas. *Acta Endocrinol. (Copenh)*, 1979; *92:* 95–104. doi:10.1530/ACTA.0.0920095.
58. Jiang, H.; Yan, W.H.; Li, C.J.; Wang, A.P.; Dou, J.T.; Mu, Y.M. Elevated White Blood Cell Count Is Associated with Higher Risk of Glucose Metabolism Disorders in Middle-Aged and Elderly Chinese People. *Int. J. Environ. Res. Public Health*, 2014; *11:* 5497. doi:10.3390/IJERPH110505497.
59. Nilsson, G.; Hedberg, P.; Öhrvik, J. White Blood Cell Count in Elderly Is Clinically Useful in Predicting Long-Term Survival. *J. Aging Res.*, 2014; *2014*. doi:10.1155/2014/475093.
60. Ren, Z.Y.; Luo, S.; Liu, L. The Positive Association between White Blood Cell Count and Metabolic Syndrome Is Independent of Insulin Resistance among a Chinese Population: A Cross-Sectional Study. *Front. Immunol*, 2023; *14*. doi:10.3389/FIMMU.2023.1104180.
61. Kabat, G.C.; Kim, M.Y.; Verma, A.K.; Manson, J.A.E.; Lin, J.; Lessin, L.; Wassertheil-Smoller, S.; Rohan, T.E. Platelet Count and Total and Cause-Specific Mortality in the Women's Health Initiative. *Ann. Epidemiol*, 2017; *27*: 274–280, doi:10.1016/J.ANNEPIDEM.2017.02.001.
62. Wang, S.; Wang, X.; Hua, X.; Jiang, S.; Xie, Y.; Liu, H. Adjusted Association between Type 2 Immunity and Low Risk Thyroid Nodules: A Retrospective Cohort Study. *BMC Endocr. Disord*, 2022; *22*. doi:10.1186/S12902-021-00917-0.
63. Ahmed, S.S.; Mohammed, A.A. Effects of Thyroid Dysfunction on Hematological Parameters: Case Controlled Study. *Ann. Med. Surg.*, 2020; *57:* 52. doi:10.1016/J.AMSU.2020.07.008.
64. Laskou, S.; Sapalidis, K.; Topalidis, C.; Koletsa, T.; Kesisoglou, I. Be(a)Ware of Leukocytosis in Papillary Thyroid Cancer. *Case Rep. Endocrinol*, 2022; *2022*. doi:10.1155/2022/5799432.
65. Alexander, R.W. Inflammation and Coronary Artery Disease. *N. Engl. J. Med.*, 1994; *331:* 468–469. doi:10.1056/NEJM199408183310709.
66. Gkrania-Klotsas, E.; Ye, Z.; Cooper, A.J.; Sharp, S.J.; Luben, R.; Biggs, M.L.; Chen, L.K.; Gokulakrishnan, K.; Hanefeld, M.; Ingelsson, E.; et al. Differential White Blood Cell Count and Type 2 Diabetes: Systematic Review and Meta-Analysis of Cross-Sectional and Prospective Studies. *PLoS One*, 2010; *5:* 13405. doi:10.1371/JOURNAL.PONE.0013405.
67. Wang, Q.; Guo, Q.; Zhou, L.; Li, W.; Yuan, Y.; Lei, W.; Liu, K.; Xu, M.; Diao, T.; Gao, H.; et al. Associations of Baseline and Changes in Leukocyte Counts with Incident Cardiovascular Events: The Dongfeng-Tongji Cohort Study. *J. Atheroscler. Thromb*, 2022; *29:* 1040. doi:10.5551/JAT.62970.
68. Wheeler, J.G.; Mussolino, M.E.; Gillum, R.F.; Danesh, J. Associations between Differential Leucocyte Count and Incident Coronary Heart Disease: 1764 Incident Cases from Seven Prospective Studies of 30 374 Individuals. *Eur. Heart J.*, 2004; *25:* 1287–1292. doi:10.1016/J.EHJ.2004.05.002.
69. Nolan, C.J.; Prentki, M. Insulin Resistance and Insulin Hypersecretion in the Metabolic Syndrome and Type 2 Diabetes: Time for a Conceptual Framework Shift. *Diabetes Vasc. Dis. Res.*, 2019; *16:* 118–127. doi:10.1177/1479164119827611.
70. Kunz, H.E.; Hart, C.R.; Gries, K.J.; Parvizi, M.; Laurenti, M.; Man, C.D.; Moore, N.; Zhang, X.; Ryan, Z.; Polley, E.C.; et al. Adipose Tissue Macrophage Populations and Inflammation Are Associated with Systemic Inflammation and Insulin Resistance in Obesity. *Am. J. Physiol. Endocrinol. Metab.*, 2021; *321:* E105–E121. doi:10.1152/AJPENDO.00070.2021.
71. Kahn, S.E.; Hull, R.L.; Utzschneider, K.M. Mechanisms Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Nature*, 2006; *444:* 840–846. doi:10.1038/NATURE05482.
72. Sinisalo, J.; Paronen, J.; Mattila, K.J.; Syrjälä, M.; Alfthan, G.; Palosuo, T.; Nieminen, M.S.; Vaarala, O. Relation of Inflammation to Vascular Function in Patients with Coronary Heart Disease. *Atherosclerosis*, 2000; *149:* 403–411, doi:10.1016/S0021-9150(99)00333-0.
73. Shankar, A.; Klein, B.E.K.; Klein, R. Relationship between White Blood Cell Count and Incident Hypertension. *Am. J. Hypertens*, 2004; *17:* 233–239. doi:10.1016/J.AMJHYPER.2003.11.005.
74. Van Beusecum, J.P.; Barbaro, N.R.; McDowell, Z.; Aden, L.A.; Xiao, L.; Pandey, A.K.; Itani, H.A.; Himmel, L.E.; Harrison, D.G.; Kirabo, A. High Salt Activates CD11c+ Antigen-Presenting Cells via SGK (Serum Glucocorticoid Kinase) 1 to Promote Renal Inflammation and Salt-Sensitive Hypertension. *Hypertens. (Dallas, Tex. 1979)*, 2019; *74:* 555–563, doi:10.1161/HYPERTENSIONAHA.119.12761.
75. Singh, K. Leucocyte Counts in Anaemia. *Indian J. Physiol. Pharmacol*, 2010; *54:* 85–88.
76. Bernard, F.; Baccini, V.; Bagneres, D.; Rossi, P.; Demoux, A.L.; Bonin-Guillaume, S.; Frances, Y.; Granel, B. [Severe Thrombocytosis and Leukocytosis Associated with Iron Deficiency Anaemia: A Case-Report]. *La Rev. Med. interne*, 2008; *29:* 662–665. doi:10.1016/J.REVMED.2008.01.006.
77. Rabah, H.; Itani, A.; Chalhoub, M. Leukocytes in Critical Patients With Asthma Exacerbation. *Cureus*, 2021; *13:* doi:10.7759/CUREUS.20520.
78. Zhu, J.; Yamane, H.; Paul, W.E. Differentiation of Effector CD4 T Cell Populations (*). *Annu. Rev.*

Immunol, 2010; *28:* 445–489. doi:10.1146/ANNUREV-IMMUNOL-030409-101212.

79. Ray, A.; Kolls, J.K. Neutrophilic Inflammation in Asthma and Association with Disease Severity. *Trends Immunol*, 2017; *38:* 942–954. doi:10.1016/J.IT.2017.07.003.
80. Xu, L.; Zeng, F.; Wang, Y.; Bai, Y.; Shan, X.; Kong, L. Prevalence and Associated Metabolic Factors for Thyroid Nodules: A Cross-Sectional Study in Southwest of China with More than 120 Thousand Populations. *BMC Endocr. Disord*, 2021; *21*. doi:10.1186/S12902-021-00842-2.
81. Paschke, R. Molecular Pathogenesis of Nodular Goiter. *Langenbeck's Arch. Surg.*, 2011; *396:* 1127–1136. doi:10.1007/S00423-011-0788-5.
82. Skou, S.T.; Mair, F.S.; Fortin, M.; Guthrie, B.; Nunes, B.P.; Miranda, J.J.; Boyd, C.M.; Pati, S.; Mtenga, S.; Smith, S.M. Multimorbidity. *Nat. Rev. Dis. Prim.*, 2022; *8.* doi:10.1038/S41572-022-00376-4.