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A retrospective database study to explore multimorbidity among patients with type 2 diabetes in a tertiary care department in Ningbo, China

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Title

A retrospective database study to explore multimorbidity among patients with type 2 diabetes in a tertiary care department in Ningbo, China

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Abstract

Objectives To determine the prevalence of multimorbidity among type 2 diabetes (T2DM) patients and factors independently associated with multimorbidity in a tertiary care department in Ningbo, China.

Design A computerised medical records database was used to conduct a retrospective cross-sectional study.

Setting Tertiary care department in Ningbo, China.

Participants The study included adult patients with T2DM and eight years of data, from 1 January 2012 to 31 December 2019.

Primary outcome measure Multimorbidity which was defined as having T2DM and at least one other chronic condition, each one was either a physical non-communicable disease of long duration (≥ 3 months), a mental health condition of long duration (≥ 3 months) or an infectious disease of long duration (≥ 3 months).

Results 4777 patients satisfied the eligibility criteria. Over eight years, the prevalence of multimorbidity among patients with T2DM was 93.7%. Those who had multimorbidity, the mean (\pm standard deviation) number of other chronic conditions was 3 (± 1). The odds of multimorbidity increased with the age of patients (18-39 years: 1; 40-59 years: odds ratio 2.80, 95% confidence interval 1.97-3.96; and ≥ 60 years: 6.04, 4.21-8.67). The odds were lower in female patients (0.63, 0.49-0.81), patients residing in rural areas (0.74, 0.58-0.94) and patients without health insurance (0.59, 0.43-0.80). The odds were higher in single/divorced/widowed patients compared to married patients (2.11, 1.32-3.37).

Conclusions A large percentage of patients with T2DM in the tertiary care department in Ningbo, China had multimorbidity and the associated factors were identified. The

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4 findings could be used in developing, evaluating and implementing interventions aimed
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6 at improving outcomes in T2DM patients with multimorbidity.

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8 **Keywords**

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10 Multimorbidity, Type 2 diabetes, China
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14 **Strengths and limitations of the study**

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- Ours was the first study to investigate multimorbidity among patients with type 2 diabetes in Ningbo and in the broader Zhejiang Province and China.
 - In our database, all the conditions are coded using the International Classification of Diseases, 10th edition (ICD-10), and we included all the chronic conditions in our study.
 - Our study had extremely low missing data and the multiple logistic regression analysis included a sample with missing data for the adjusted variable.
 - Being a cross-sectional study, the causal relationship between variables and multimorbidity could not be determined.
 - Our study had the usual routinely collected data issues as an existing medical records database was used – its main purpose is medical management and not research.

Introduction

Ningbo is an economically developed Chinese city in the Zhejiang Province. Non-communicable diseases, mental health conditions and infectious diseases are prevalent in the city.¹ One such non-communicable disease is type 2 diabetes (T2DM), a complex metabolic disorder. China has the largest T2DM epidemic in the world, and in Ningbo, its prevalence in 40+ years adults is 21%.² In real-life, T2DM is rarely presented in isolation and is accompanied by other chronic conditions.³

Globally, research on multimorbidity is a conceptually new area. Multimorbidity is commonly defined as having two or more chronic conditions in the same individual.⁴ It accelerates the progression of individual chronic conditions;⁵ brings in other physical and mental conditions and even premature mortality;^{6 7} negatively affects the overall health, wellbeing and functioning;^{8 9} and leads to high treatment burden, healthcare utilisation and expenditure and loss of economic output.¹⁰⁻¹³

To date, no study has been undertaken to investigate multimorbidity among patients with T2DM in Ningbo. The study objectives were to determine the prevalence of multimorbidity among patients with T2DM and factors independently associated with multimorbidity. This knowledge could be used in developing, evaluating and implementing interventions aimed at improving outcomes in T2DM patients with multimorbidity.

Methods

Study location, study design, data source and study period

We conducted the study in a tertiary care department in Ningbo, China - Department of Endocrinology and Metabolism, Ningbo First Hospital. This tertiary care hospital is responsible for the delivery of specialist healthcare services and for medical education and research.^{14 15} Local people and people from surrounding areas can visit this hospital as no referral is required from the general practitioner.¹⁴ An existing computerised medical records database was used for conducting this cross-sectional

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4 study. The database contains information on all inpatients. Data are entered by the
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6 medico-nursing team. The quality check of the data and the overall database
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8 management are the responsibility of an independent group of hospital staff. All the
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10 conditions are coded using the International Classification of Diseases, 10th edition
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12 (ICD-10). This retrospective study included eight years of data, from 1 January 2012
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14 to 31 December 2019, and information was available on 6755 patients.
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17 ***Study population and study inclusion and exclusion criteria***

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19 Adult patients (≥ 18 years) with T2DM were included. If a patient was admitted more
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21 than once during the study period, data pertinent to the last admission were extracted
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23 to obtain the most up to date information on chronic conditions. Individuals with
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25 gestational diabetes, type 1 diabetes, secondary diabetes and unknown type of
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27 diabetes were excluded.
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30 ***Study variables***

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32 We extracted and categorised the following information from the database:
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- 35 • age (18-39 years, 40-59 years or ≥ 60 years),
 - 36 • sex (male or female),
 - 37 • education (university/college, class 7-12, class 1-6 or no qualification),
 - 38 • occupation (manual worker (i.e., more physical work than mental work), non-
39 manual worker (i.e., more mental work than physical work) or never
40 worked/retired),
 - 41 • marital status (married or single/divorced/widowed),
 - 42 • residence (urban or rural using the “hukou” system (i.e., the Chinese household
43 registration system)),
 - 44 • health insurance,
 - 45 • smoking (current status),
 - 46 • alcohol drinking (current status),
 - 47 • duration of T2DM (≤ 1 year, $>1-5$ years, $>5-10$ years or >10 years),
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- blood glucose level (glycated haemoglobin (HbA1c <7% (good) or ≥7% (poor)), estimated using the high-performance liquid chromatographic (HPLC) method and D-10 Hemoglobin Analyzer (Bio-Rad, USA)).

In addition, information on multimorbidity was extracted. Multimorbidity was defined as having T2DM and at least one other chronic condition, each one was either a physical non-communicable disease of long duration (≥3 months), a mental health condition of long duration (≥3 months) or an infectious disease of long duration (≥3 months).^{16 17} In our study, a T2DM specific complication, such as diabetic neuropathy, diabetic nephropathy, diabetic retinopathy or diabetic foot, was not counted as a chronic condition in multimorbidity. This is because these microvascular complications are in relation to the index disease (i.e., T2DM).^{18 19}

Ethics

The Research Ethics Committee of Ningbo First Hospital, China approved the study (2020-R106).

Patient and public involvement

Patient and public were not involved in the study.

Statistical analyses

We calculated numbers and percentages for categorical variables and means and standard deviations (SDs) for normally distributed continuous variables. We used simple logistic regression method to investigate the association between different variables and multimorbidity. We developed a multiple logistic regression model to find any independent association. For this, we used the backward stepwise regression analysis and included all the variables. Additionally, we did a sensitivity analysis - in the multiple logistic regression model, we included only those variables that had a p-value of ≤0.20 in simple logistic regressions. We calculated odds ratios (ORs) and 95% confidence intervals (CIs). We used IBM SPSS Statistics version 26.0 for Windows for statistical analyses.

Results

4777 patients satisfied the eligibility criteria. The mean (\pm SD) age of patients was 64.2 (\pm 14.2) years and around 52% (n=2482) of them were male. Over eight years, the prevalence of multimorbidity among patients with T2DM was 93.7%. The year-wise (from 2012 to 2019) prevalence was 96.9%, 95.0%, 92.9%, 95.5%, 93.2%, 91.5%, 94.0% and 93.6%, respectively.

Figure 1 shows the number of other chronic conditions in our study (in addition to T2DM). Those who had multimorbidity, the mean (\pm SD) number of other chronic conditions was 3 (\pm 1). 55.6% of patients had \geq 3 other chronic conditions. Table 1 reports the most common other chronic conditions in our study (in addition to T2DM). Essential hypertension (49.4%), disorders of lipoprotein metabolism and other lipidaemias (33.7%), nontoxic thyroid nodule (22.8%), fatty change of liver (20.6%) and cataract (10.7%) were the five most prevalent chronic conditions.

Table 2 reports the characteristics of the study participants. We found that multimorbidity was associated with age, sex, education, occupation, marital status, residence, health insurance and duration of T2DM. Table 3 reports the multiple backward stepwise logistic regression analysis for determining factors independently associated with multimorbidity. The odds of multimorbidity increased with the age of patients (18-39 years: 1; 40-59 years: OR 2.80, 95% CI 1.97-3.96; and \geq 60 years: 6.04, 4.21-8.67). The odds were lower in female patients (0.63, 0.49-0.81), patients residing in rural areas (0.74, 0.58-0.94) and patients without health insurance (0.59, 0.43-0.80). The odds were higher in single/divorced/widowed patients compared to married patients (2.11, 1.32-3.37). In the sensitivity analysis, we found the same results.

Discussion

In our tertiary care department in Ningbo, China, around 94% of patients with T2DM had multimorbidity. We could not find any similar study conducted among patients with

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4 T2DM in China, but in two other studies conducted among community-dwelling and
5 hospitalised older adults, the prevalence of multimorbidity was around 49% and 69%,
6 respectively.^{20 21} This could be due to the difference in the population characteristics
7 and the way chronic conditions were measured. Several studies have been conducted
8 on this topic in high-income countries like the United States and in Europe.²²⁻²⁶ All these
9 studies, including our study, have highlighted the fact that multimorbidity is high among
10 patients with T2DM.²²⁻²⁶ In our study, those who had multimorbidity, the average
11 number of other chronic conditions was three. Around 56% of patients had ≥ 3 other
12 chronic conditions, and this is similar to what other studies have found.^{22 23} A
13 systematic review and meta-analysis summarising the prevalence and associated
14 factors of multimorbidity in different geographical locations will be helpful.

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27 In our study, essential hypertension, disorders of lipoprotein metabolism and other
28 lipidaemias, nontoxic thyroid nodule, fatty change of liver and cataract were the five
29 most prevalent chronic conditions. The overall profile is similar to what other studies
30 have found.^{23,24} The pathophysiological connection between T2DM and cardiovascular
31 diseases is well known.^{27 28} Similarly, T2DM and thyroid diseases are the two most
32 common chronic conditions of the endocrine system, and patients with T2DM are more
33 likely to develop thyroid nodule, which could be due to insulin resistance.^{29 30} In our
34 population and setting, around 72% of patients with T2DM were prescribed
35 polypharmacy.³¹ A specific medicine may be used for managing a chronic condition
36 and the same may be contraindicated in another chronic condition. This needs to be
37 taken into consideration when managing multimorbidity among patients with T2DM.³²
38 This point is valid even for preventing new chronic conditions like cardiovascular
39 diseases among patients with T2DM. For example, the usage of a new generation of
40 hypoglycaemic medicines, such as glucagon-like peptide 1 (GLP-1) receptor agonists
41 and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, reduces the risk of
42 cardiovascular diseases.^{33 34}

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4 We found that the odds of multimorbidity increased with the age of patients. Age is one
5 of the most well studied and consistent determinants of multimorbidity.^{12 35} Age-related
6 organ degeneration is a natural process and can bring in many chronic conditions.³⁶
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8 However, it should be noted that multimorbidity is not equal to ageing and limited to
9 older age alone.³⁷ In our study, the prevalence of multimorbidity was around 80% and
10 91% in the 18-39 and 40-59 years age groups, respectively. We found that the odds
11 of multimorbidity were lower in females than in males. The finding is consistent with
12 other studies.^{22 25} This could be due to the differences at the biological level. Another
13 potential reason could be reporting differences in sex-specific chronic conditions. For
14 example, female patients with T2DM often present atypical symptoms of
15 cardiovascular diseases.³⁸ Even the standard non-invasive diagnostic tests perform
16 better in men than in women.³⁹ All these hinder the diagnosis of cardiovascular
17 diseases in women. Another example is benign prostatic hyperplasia, which was one
18 of the most common chronic conditions in our study. This chronic condition was
19 diagnosed because of the compulsory ultrasound scan of the urinary system of
20 patients with T2DM at our hospital for possible kidney comorbidities. In comparison,
21 the gynaecological examination is not a routine examination in women with T2DM.
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39 We found that the odds of multimorbidity were lower in patients residing in rural areas
40 compared to urban areas. The finding is consistent with other studies.^{40 41} This could
41 be due to the economic growth, urbanisation and its negative consequences like
42 unhealthy lifestyle.⁴²⁻⁴⁴ The link between an unhealthy lifestyle and chronic conditions
43 (particularly non-communicable diseases) is well established.⁴⁵ A similar association
44 with multimorbidity has also emerged.⁴⁶ The other reason could be – rural patients in
45 China have limited access to healthcare and thus, may undergo fewer diagnostic tests
46 and confirmation of chronic conditions.⁴⁷
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56 We found that the odds of multimorbidity were lower in patients without health
57 insurance compared to those with health insurance. This could be due to the fact that
58 over 90% of the Chinese population have some sort of health insurance⁴⁸ and these
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4 patients may undergo more diagnostic tests (within the scope of their health insurance
5 policy) and confirmation of chronic conditions.⁴⁹ We found that the odds of
6 multimorbidity were higher in single/divorced/widowed patients compared to married
7 patients. The finding is consistent with other studies.^{50 51} In general, the spouse of a
8 married patient looks after them, both physically and mentally, and this could help them
9 in managing their existing chronic conditions and preventing new chronic conditions to
10 develop.^{52 53}

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19 Apart from the already mentioned strengths and weaknesses, the study has some
20 more strengths and weaknesses. Multimorbidity is a less explored area in China, and
21 to the best of our knowledge, this was the first study to explore multimorbidity among
22 patients with T2DM in Ningbo and in the broader Zhejiang Province and China. Unlike
23 other studies which included only older adults,^{20 21 51} we included adults without any
24 age restriction. It should be noted that multimorbidity is not equal to ageing and limited
25 to older age alone.³⁷ Unlike other studies where chronic conditions in multimorbidity
26 were self-reported by patients using a predetermined list of selected chronic
27 conditions,^{20 24} we used a holistic approach. In the database, all the conditions are
28 coded using the International Classification of Diseases, 10th edition (ICD-10), and we
29 included all the chronic conditions in our study. This also minimised the possibility of
30 recall bias in our study. Our study had extremely low missing data and the multiple
31 logistic regression analysis included a sample with missing data for the adjusted
32 variable. Being a cross-sectional study, the causal relationship between variables and
33 multimorbidity could not be determined. We propose conducting a longitudinal study
34 to explore the effect of various factors on multimorbidity, including factors considered
35 in this study and some other factors like physical activity and diet that are not present
36 in our database and could not be adjusted for in the models. Our study had the usual
37 routinely collected data issues as an existing medical records database was used – its
38 main purpose is medical management and not research. The findings of our hospital-
39 based study could be valid in similar populations and settings. We suggest conducting
40 a population-based study that might show a distinct picture of the issue.

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6 In conclusion, we found that a large percentage of patients with T2DM in the tertiary
7 care department in Ningbo, China had multimorbidity and identified the associated
8 factors. The findings could be used in developing, evaluating and implementing
9 interventions aimed at improving outcomes in T2DM patients with multimorbidity.
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23 entry. XL contributed to data cleaning. XL, KC, SX, YC, MX, LL and JL revised it
24 critically for important intellectual content and approved the final version.
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39 **Competing interests** None declared.
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43 **Ethics approval** The Research Ethics Committee of Ningbo First Hospital, China
44 approved the study (2020-R106).
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49 **Data sharing statement** The dataset will be available upon request unless there are
50 legal or ethical reasons for not doing so.
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Figure 1. Number of other chronic conditions in our study (in addition to T2DM).

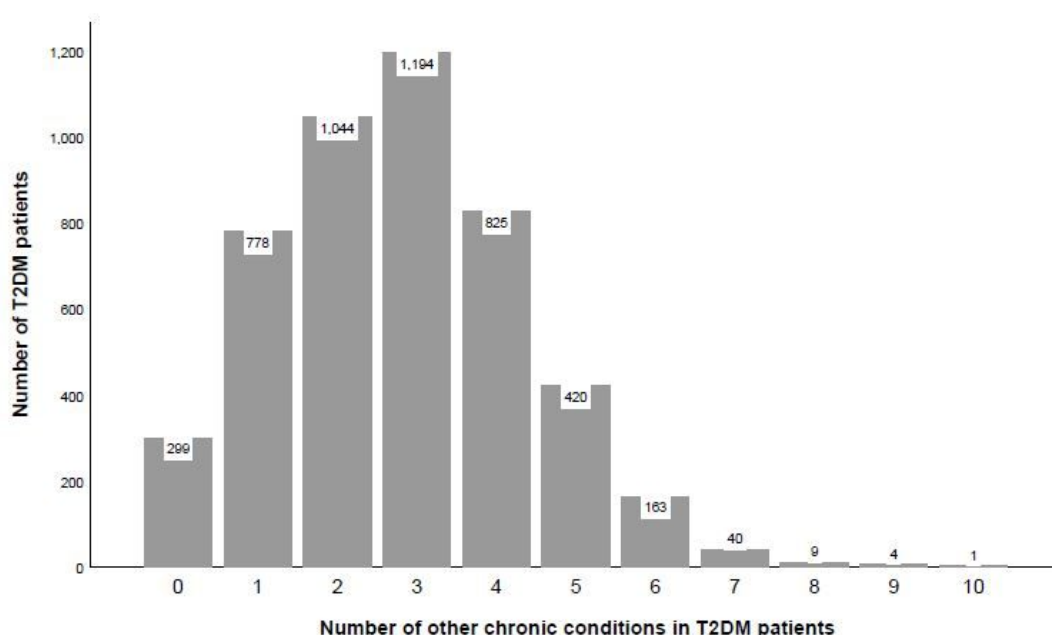


Table 1. Most common other chronic conditions in our study (in addition to T2DM).

Most common other chronic conditions (based on ICD-10 classification)	Patients with T2DM n (%)
Essential hypertension (I10)	2362 (49.4)
Disorders of lipoprotein metabolism and other lipidaemias (E78)	1612 (33.7)
Nontoxic thyroid nodule (E04)	1088 (22.8)
Fatty (change of) liver (K76)	984 (20.6)
Cataract (H26)	512 (10.7)
Chronic ischemic heart disease (I25)	455 (9.5)
Atherosclerosis (I70)	411 (8.6)
Osteoporosis (M81)	348 (7.3)
Cerebral infarction (I63)	341 (7.1)
Benign prostatic hyperplasia (N40)	303 (12.2*)

Abnormal findings on diagnostic imaging of lung (R91)	287 (6.0)
Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (M51)	260 (5.4)
Obesity (E66)	177 (3.7)
Cervical disc disorders (M50)	161 (3.4)
Chronic viral hepatitis (B18)	138 (2.9)
Sleep disorders (G47)	135 (2.8)
Gout (M10)	132 (2.8)
Disorders of purine and pyrimidine metabolism (E79)	127 (2.7)
Atrial fibrillation and flutter (I48)	118 (2.5)
Gastro-esophageal reflux disease (K21)	111 (2.3)

*In 2482 males.

Table 2. Characteristics of the study participants.

	Total (4777)	Multimorbidity No (299) n (%)	Multimorbidity Yes (4478) n (%)	Unadjusted OR (95% CI)	P value
Age (years)					<0.001
18-39	308	63 (20.5)	245 (79.5)	1	
40-59	1360	120 (8.8)	1240 (91.2)	2.66 (1.90,3.71)	
≥60	3109	116 (3.7)	2993 (96.3)	6.64 (4.75,9.26)	
Sex					0.008
Male	2482	133 (5.4)	2349 (94.6)	1	
Female	2295	166 (7.2)	2129 (92.8)	0.73 (0.57,0.92)	
Education					0.005
University/college	545	47 (8.6)	498 (91.4)	1	
Class 7-12	1927	136 (7.1)	1791 (92.9)	1.24 (0.88,1.76)	
Class 1-6	1574	80 (5.1)	1494 (94.9)	1.76 (1.21,2.56)	
No qualification	731	36 (4.9)	695 (95.1)	1.82 (1.16,2.86)	
Occupation					<0.001
Manual worker	1088	74 (6.8)	1014 (93.2)	1	
Non-manual worker	1884	152 (8.1)	1732 (91.9)	0.83 (0.62,1.10)	
Never worked/retired	1805	73 (4.0)	1732 (96.0)	1.73 (1.24,2.41)	
Marital status					0.008
Married	4207	278 (6.6)	3929 (93.4)	1	
Single/divorced/widowed	570	21 (3.7)	549 (96.3)	1.85 (1.18,2.91)	
Residence					<0.001
Urban	2815	145 (5.2)	2670 (94.8)	1	
Rural	1962	154 (7.8)	1808 (92.2)	0.64 (0.50,0.81)	
Health insurance					<0.001
Yes	4211	232 (5.5)	3979 (94.5)	1	
No	564	67 (11.9)	497 (88.1)	0.43 (0.33,0.58)	
Smoking (current status)					0.073
No	3714	245 (6.6)	3469 (93.4)	1	

Yes	1063	54 (5.1)	1009 (94.9)	1.32 (0.98,1.79)	
Alcohol drinking (current status)					0.713
No	4169	263 (6.3)	3906 (93.7)	1	
Yes	608	36 (5.9)	572 (94.1)	1.07 (0.75,1.53)	
Duration of T2DM (years)					<0.001
≤1	981	93 (9.5)	888 (90.5)	1	
>1-5	880	60 (6.8)	820 (93.2)	1.43 (1.02,2.01)	
>5-10	1247	74 (5.9)	1173 (94.1)	1.66 (1.21,2.28)	
>10	1669	72 (4.3)	1597 (95.7)	2.32 (1.69,3.19)	
Blood glucose level (HbA1c)					0.458
<7%	899	64 (7.1)	835 (92.9)	1	
≥7%	3748	226 (6.0)	3522 (94.0)	1.19 (0.90,1.59)	
Unknown	130	9 (6.9)	121 (93.1)	1.03 (0.50,2.12)	

Table 3. Multiple backward stepwise logistic regression analysis for determining factors independently associated with multimorbidity.

	Adjusted OR (95% CI)	P value
Age (years)		<0.001
18-39	1	
40-59	2.80 (1.97,3.96)	
≥60	6.04 (4.21,8.67)	
Sex		<0.001
Male	1	
Female	0.63 (0.49,0.81)	
Marital status		0.002
Married	1	
Single/divorced/widowed	2.11 (1.32,3.37)	
Residence		0.014
Urban	1	
Rural	0.74 (0.58,0.94)	
Health insurance		<0.001
Yes	1	
No	0.59 (0.43,0.80)	

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	6, Table2
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Table2
		(b) Indicate number of participants with missing data for each variable of interest	Table2
Outcome data	15*	Report numbers of outcome events or summary measures	7, Figure 1, Table1, Table2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, Table2
		(b) Report category boundaries when continuous variables were categorized	7, Table2, Table3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7,8,9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7,8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence of comorbidities and their associated factors in patients with type 2 diabetes at a tertiary care department in Ningbo, China: a cross-sectional study

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Title

Prevalence of comorbidities and their associated factors in patients with type 2 diabetes at a tertiary care department in Ningbo, China: a cross-sectional study

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Abstract

Objectives To determine the prevalence of comorbidities in patients with type 2 diabetes (T2DM) and identify the factors independently associated with comorbidities in a tertiary care department in Ningbo, China.

Design A computerised medical records database was used to conduct a cross-sectional study.

Setting The study was conducted in a tertiary care department in Ningbo, China.

Participants The study was conducted on adult patients with T2DM, and it included eight years of data, from 1 January 2012 to 31 December 2019.

The primary outcome measure Comorbidity was defined as the co-existence of at least one other chronic condition, i.e., either a physical non-communicable disease (duration ≥ 3 months), a mental health condition (duration ≥ 3 months), or an infectious disease (duration ≥ 3 months).

Results In total, 4777 patients with T2DM satisfied the eligibility criteria. Over eight years, the prevalence of comorbidities was 93.7%. The odds of comorbidities increased with the age of patients (18–39 years: 1; 40–59 years: odds ratio 2.80, 95% confidence interval 1.98–3.96; 60–69 years: 4.43, 3.04–6.44; and ≥ 70 years: 10.97, 7.17–16.77). The odds were lower in female patients (0.66, 0.51–0.84), patients residing in rural areas (0.75, 0.59–0.95), and patients without health insurance (0.62, 0.46–0.83). The odds were higher in single/divorced/widowed patients compared to those in married patients (1.95, 1.21–3.12).

Conclusions A large percentage of patients with T2DM in the tertiary care department in Ningbo, China, had comorbidities, and the factors associated with comorbidities were identified. The findings could be used in developing, evaluating, and

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4 implementing interventions aimed at improving outcomes in patients with T2DM with
5 comorbidities.
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7 **Keywords**

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9 comorbidity, type 2 diabetes, China
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13 **Strengths and limitations of the study**

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15 Ours was the first study to investigate comorbidities in patients with type 2 diabetes in
16 Ningbo and the broader Zhejiang Province of China.
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19 We included all the chronic conditions in our study; they were coded using the
20 International Classification of Diseases, 10th edition (ICD-10) in our database.
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23 Our study had extremely low missing data and the multiple logistic regression analysis
24 included a sample with missing data for the adjusted variable.
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27 As it was a cross-sectional study, the causal relationship between the variables and
28 the comorbidities could not be determined.
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31 The high prevalence of comorbidities in our study could be due to the study setting
32 (i.e., hospital).
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INTRODUCTION

Ningbo is an economically developed Chinese city in Zhejiang Province. The population of the city is approximately 8.2 million.[1] Non-communicable diseases, mental health conditions, and infectious diseases are prevalent in the city.[2] Of these, one of the most prevalent non-communicable diseases is type 2 diabetes (T2DM). T2DM is a chronic complex metabolic disorder. China has the largest T2DM epidemic in the world, and in Ningbo, its prevalence in adults \geq 40 years of age is 21%.[3] In Ningbo, the diabetes-related mortality is 14.5 per 100,000 population.[4]

There is no international consensus regarding the best way to define comorbidity. It is usually defined as the co-existence of other conditions with an index condition (i.e., the main condition under study) where these other conditions are not consequences of the index condition.[5-7] Comorbidities accelerate the progression of individual conditions, encourage the development of other physical and mental conditions, and even lead to premature mortality.[8-10] Moreover, they negatively affect overall health, wellbeing, and functioning.[11, 12] Additionally, they lead to high treatment burden, high healthcare utilisation and expenditure, and loss of economic output.[13, 14] In real life, T2DM is rarely presented in isolation and is always accompanied by comorbidity.[15, 16]

To date, no study has been undertaken to investigate comorbidities in patients with T2DM in Ningbo. The study objectives were to determine the prevalence of comorbidities in patients with T2DM and identify the factors independently associated with comorbidities. This knowledge could be used in developing, evaluating, and implementing interventions aimed at improving outcomes in patients with T2DM with comorbidities.

METHODS

Study location, study design, data source, and study period

We conducted the study in a tertiary care department, the Department of Endocrinology and Metabolism, Ningbo First Hospital, in Ningbo, China. This tertiary care hospital delivers speciality healthcare services, provides medical education, and conducts research.[17,18] Locals and people from the surrounding areas visit this hospital as no referral is required from the general practitioner.[17] An existing computerised medical records database was used for conducting this cross-sectional study. This database contained information on all inpatients. Since it was a real-time database, new patients were added continuously. Data were entered by the medico-nursing team and an independent group of the hospital staff was responsible for assessing the quality of the data and overall database management. All the conditions were coded using the International Classification of Diseases, 10th edition (ICD-10). This retrospective study included eight years of data, from 1 January 2012 to 31 December 2019, and the information was available on 6755 patients.

Study population and study inclusion and exclusion criteria

Adult patients (≥ 18 years) with T2DM were included. If a patient was admitted more than once during the study period, data pertinent to the last admission were extracted to obtain the most recent information on health conditions. Individuals with gestational diabetes, type 1 diabetes, secondary diabetes, and unknown types of diabetes were excluded.

Study variables

We extracted and categorised the following information from the database:

- age (18–39 years, 40–59 years, 60–69 years or ≥ 70 years),
- sex (male or female),
- education (university/college, class 7–12, class 1–6, or no qualification),

- occupation (manual worker [i.e., more physical work than mental work], non-manual worker [i.e., more mental work than physical work], or never worked/retired),
- marital status (married or single/divorced/widowed),
- residence (urban or rural using the “hukou” system i.e., the Chinese household registration system),
- health insurance,
- smoking (current status),
- alcohol consumption (current status),
- duration of T2DM (\leq 1 year, > 1–5 years, > 5–10 years, or > 10 years), and
- blood glucose level (glycated haemoglobin [HbA1c < 7% (good) or \geq 7% (poor)], estimated using the high-performance liquid chromatographic method and D-10 Haemoglobin Analyser [Bio-Rad, USA]). In China, the recommended HbA1c treatment target did not change over the study period (< 7% for most patients with T2DM).[19-21]

In addition, information on comorbidities was extracted. The index condition was T2DM. Comorbidity was defined as the co-existence of at least one other chronic condition, i.e., either a physical non-communicable disease (duration \geq 3 months), a mental health condition (duration \geq 3 months), or an infectious disease (duration \geq 3 months).[5-7] T2DM-specific complications (i.e., microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy/foot) were excluded as these were consequences of the index condition; hence, they were not considered as comorbidities.[6]

Ethics

The Research Ethics Committee of the Ningbo First Hospital, China, approved this study (2020-R106). The researchers had no access to information that could identify individual patients during the data analyses. No informed consent was required as per

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4 research ethics rules.
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7 **Patient and public involvement**

8 Patients and public were not involved in the study.
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12 **Statistical analyses**

13 We calculated numbers and percentages for categorical variables, and means and
14 standard deviations (SDs) for normally distributed continuous variables. We used a
15 simple logistic regression method to investigate the association between the different
16 variables and comorbidities. We developed a multiple logistic regression model to
17 identify any independent associations. For this, we used backward stepwise
18 regression analysis and included all the variables. Additionally, we performed a
19 sensitivity analysis — in the multiple logistic regression model, we included only those
20 variables that had a p-value ≤ 0.20 in simple logistic regressions. We calculated odds
21 ratios (ORs) and 95% confidence intervals (CIs). We used IBM SPSS Statistics version
22 26.0 for Windows for statistical analyses.
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37 **RESULTS**

38 A total of 4777 patients with T2DM satisfied the eligibility criteria. The mean (\pm SD) age
39 of patients was 64.2 (\pm 14.2) years, and approximately 52% (n=2482) of them were
40 men. The mean (\pm SD) HbA1c level was 9.2% (\pm 2.4%). Over eight years, the
41 prevalence of comorbidities was 93.7%. The year-wise prevalences from 2012 to 2019
42 were 96.9%, 95.0%, 92.9%, 95.5%, 93.2%, 91.5%, 94.0%, and 93.6%, respectively.
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51 Figure 1 shows the number of comorbidities in our study. The mean (\pm SD) number of
52 comorbidities was 3 (\pm 1). Figure 2 shows the number of comorbidities in our study in
53 the different age groups. In the ≥ 70 years age group, 68.5% (1247) had ≥ 3
54 comorbidities, whereas the prevalences were only 33.1% (102), 43.5% (592), and 55.5%
55 (715) in the 18–39, 40–59, and 60–69 years age groups, respectively. Table 1 reports
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4 the most common comorbidities in our study. Essential hypertension (49.4%),
5 disorders of lipoprotein metabolism and other lipidaemias (33.7%), nontoxic thyroid
6 nodule (22.8%), fatty change of liver (20.6%), and cataract (10.7%) were the five most
7 prevalent comorbidities.
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13 Table 2 reports the characteristics of the study participants. We found that the
14 comorbidities were associated with age, sex, education, occupation, marital status,
15 residence, health insurance, and the duration of T2DM. Table 3 reports the multiple
16 backward stepwise logistic regression analysis for determining factors independently
17 associated with the comorbidities. The odds of comorbidities increased with the age of
18 patients (18–39 years: 1; 40–59 years: OR 2.80, 95% CI 1.98–3.96; 60–69 years: 4.43,
19 3.04–6.44; and ≥70 years: 10.97, 7.17–16.77). The odds were lower in female patients
20 (0.66, 0.51–0.84), patients residing in rural areas (0.75, 0.59–0.95), and patients
21 without health insurance (0.62, 0.46–0.83). The odds were higher in
22 single/divorced/widowed patients compared to married patients (1.95, 1.21–3.12). We
23 obtained similar results in the sensitivity analysis.
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38 **DISCUSSION**

39 In our tertiary care department in Ningbo, China, approximately 94% of the patients
40 with T2DM had comorbidities and this influenced the overall management. In a
41 previous study, we found that approximately 72% of the patients with T2DM were
42 prescribed polypharmacy.[22] There are no similar studies on comorbidities conducted
43 in patients with T2DM in China published in the English language. However, we found
44 two similar studies published in Mandarin: one on patients with diabetes at a
45 community health centre and another on outpatients with T2DM at a tertiary care
46 hospital.[23, 24] The corresponding prevalence figures were around 95% and 73%,
47 respectively. The different prevalence figures could be explained by the differences in
48 population characteristics, the study setting, and the definition of comorbidity applied.
49 Several studies have been conducted on this subject in high-income countries such as
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4 the United States and European countries.[25-29] All these studies, and also our study,
5 have highlighted the fact that comorbidities are highly prevalent in patients with T2DM.
6 A systematic review and meta-analysis of the prevalence and the factors associated
7 with comorbidities in patients with T2DM in different geographical locations will be
8 helpful.
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15 Comorbidities are not synonymous with complications.[6] In a previous study on the
16 vascular complications of T2DM, we included microvascular complications (i.e.,
17 diabetic retinopathy, nephropathy, and neuropathy/foot) and macrovascular
18 complications (i.e., coronary heart disease, stroke, and peripheral arterial disease) and
19 found that more than half of the patients with T2DM had vascular complications.[30] In
20 the present study, we explored comorbidities in patients with T2DM using a
21 recommended definition. Comorbidity was defined as the co-existence of at least one
22 other chronic condition, either a physical (non-communicable/infectious disease) or
23 mental health condition.[5-7] Unlike the previous study, in the present study,
24 microvascular complications were excluded, as these were consequences of T2DM
25 and should not be considered as comorbidities.[6]
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39 We found that the odds of comorbidities increased with age in patients with T2DM. Age
40 is one of the most well-studied and consistent determinants of comorbidities.[25, 28,
41 31] Age-related organ degeneration is a natural process and can lead to the
42 development of many health conditions.[32] However, it should be noted that
43 comorbidities do not correspond with age and they are not limited to the older
44 population alone.[33] In our study, the prevalences of comorbidities were around 80%
45 and 91% in the 18–39 and 40–59 years age groups, respectively. We found that the
46 odds of comorbidities were lower in female patients with T2DM compared with those
47 in their male counterparts. This finding is consistent with other studies.[25, 28] This
48 could be due to differences at the biological level. Another potential reason could be
49 the reporting differences in sex-specific health conditions. For example, female
50 patients with T2DM often present with atypical symptoms of cardiovascular
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4 diseases.[34] Additionally, the standard non-invasive diagnostic tests perform better in
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6 men than in women.[35] All these hinder the diagnosis of cardiovascular diseases in
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8 women. Another example is benign prostatic hyperplasia, one of the most common
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10 comorbidities in our study. This comorbidity was diagnosed because of the compulsory
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12 ultrasound scan of the urinary system of patients with T2DM at our hospital for possible
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14 kidney diseases. In comparison, the gynaecological examination is not a routine
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16 examination in women with T2DM.

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19 We found that the odds of comorbidities were lower in patients with T2DM residing in
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21 rural areas compared to those in urban areas. This could be due to economic growth,
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23 urbanisation, and its negative consequences such as an unhealthy lifestyle.[36-38]
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25 The link between an unhealthy lifestyle and chronic conditions (particularly non-
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27 communicable diseases) is well established.[39] A similar association has also
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29 emerged with comorbidities.[23, 40] Another reason could be that rural patients in
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31 China have limited access to healthcare and thus, they may undergo fewer diagnostic
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33 tests and obtain fewer confirmations of health conditions.[41] We found that the odds
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35 of comorbidities were lower in patients with T2DM without health insurance compared
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37 to those with health insurance. This could be due to the fact that over 90% of the
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39 Chinese population have some sort of health insurance,[42] and these patients may
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41 undergo more diagnostic tests (within the scope of their health insurance policy) and
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43 obtain confirmation of a range of health conditions.[43] We found that the odds of
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45 comorbidities were higher in single/divorced/widowed patients with T2DM compared
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47 with those in married patients. In general, the spouses of married patients provide both
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49 physical and mental support to them, and this could help them manage their existing
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51 health conditions and prevent new ones from emerging.[44,45]

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54 This study has several strengths and weaknesses. Comorbidity is a less-explored area
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56 in China, and to the best of our knowledge, this was the first study to explore
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58 comorbidities in patients with T2DM in Ningbo and the broader Zhejiang Province. The
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60 quality of our routinely collected data was good. Unlike other studies where

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4 comorbidities in T2DM were self-reported by the patients with T2DM using a
5 predetermined list of selected comorbidities,[23, 24] we used a holistic approach. All
6 the conditions were coded using the International Classification of Diseases, 10th
7 edition (ICD-10) in our database, and we included all the chronic conditions in our
8 study. This also minimised the possibility of recall bias in our study. Our study had
9 extremely low missing data; only HbA1c data were missing in 130 patients out of 4777
10 (i.e., 2.7%). Multiple logistic regression analysis included a sample with missing data
11 for the adjusted variable. Since it was a cross-sectional study, the causal relationship
12 between variables and comorbidities could not be determined. We propose to conduct
13 a longitudinal study to explore the effects of various factors on comorbidities, including
14 factors considered in this study and other factors such as physical activity and diet that
15 were not present in our database and could not be adjusted for in the models. In our
16 study, the high prevalence of comorbidities could be due to the study setting (i.e.,
17 hospital). The findings of our hospital-based study could be valid in similar settings.
18 We suggest conducting a population-based study that might provide a distinct picture
19 of the issue in Ningbo.
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37 In conclusion, we found that a large percentage of patients with T2DM in the tertiary
38 care department in Ningbo, China, had comorbidities, and we also identified the factors
39 associated with comorbidities. The findings could be used in developing, evaluating,
40 and implementing interventions aimed at improving outcomes in patients with T2DM
41 with comorbidities.
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49 management and organisation of the original data.
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54 **CONTRIBUTORS** JL and KC designed the study. XL and KC analysed the data and
55 wrote the first draft of the manuscript. SX and YC contributed to patient registration
56 and data entry. XL contributed to data cleaning. XL, KC, SX, YC, MX, LL and JL revised
57 it critically for important intellectual content and approved the final version.
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8 Development of Ningbo Science and Technology Bureau (Grant No. 2019C50094).
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13 **COMPETING INTERESTS** None declared.
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17 **ETHICS APPROVAL** The Research Ethics Committee of Ningbo First Hospital, China
18 approved the study (2020-R106).
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23 **DATA SHARING STATEMENT** The dataset will be available upon request unless
24 there are legal or ethical reasons for not doing so.
25

26 27 28 **REFERENCES**

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30 Social Development in Ningbo, China, 2018.
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Figure 1. Number of comorbidities in our study.

Figure 2. Number of comorbidities in our study in the different age groups.

Table 1. Most common comorbidities in our study.

Most common comorbidities (based on ICD-10 classification)	Patients with T2DM n (%)
Essential hypertension (I10)	2362 (49.4)
Disorders of lipoprotein metabolism and other lipidaemias (E78)	1612 (33.7)
Nontoxic thyroid nodule (E04)	1088 (22.8)
Fatty (change of) liver (K76)	984 (20.6)
Cataract (H26)	512 (10.7)
Chronic ischemic heart disease (I25)	455 (9.5)
Atherosclerosis (I70)	411 (8.6)
Osteoporosis (M81)	348 (7.3)
Cerebral infarction (I63)	341 (7.1)
Benign prostatic hyperplasia (N40)	303 (12.2*)
Abnormal findings on diagnostic imaging of lung (R91)	287 (6.0)
Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (M51)	260 (5.4)
Obesity (E66)	177 (3.7)
Cervical disc disorders (M50)	161 (3.4)
Chronic viral hepatitis (B18)	138 (2.9)
Sleep disorders (G47)	135 (2.8)
Gout (M10)	132 (2.8)
Disorders of purine and pyrimidine metabolism (E79)	127 (2.7)
Atrial fibrillation and flutter (I48)	118 (2.5)
Gastro-oesophageal reflux disease (K21)	111 (2.3)

*In 2482 males.

Table 2. Characteristics of the study participants.

	Total (4777)	Comorbidity No (299) n (%)	Comorbidity Yes (4478) n (%)	Unadjusted OR (95% CI)	P value
Age (years)					<0.001
18-39	308	63 (20.5)	245 (79.5)	1	
40-59	1360	120 (8.8)	1240 (91.2)	2.66 (1.90,3.71)	
60-69	1289	75 (5.8)	1214 (94.2)	4.16 (2.90,5.98)	
≥70	1820	41 (2.3)	1779 (97.7)	11.16 (7.37,16.90)	
Sex					0.008
Male	2482	133 (5.4)	2349 (94.6)	1	
Female	2295	166 (7.2)	2129 (92.8)	0.73 (0.57,0.92)	
Education					0.005
University/college	545	47 (8.6)	498 (91.4)	1	
Class 7-12	1927	136 (7.1)	1791 (92.9)	1.24 (0.88,1.76)	
Class 1-6	1574	80 (5.1)	1494 (94.9)	1.76 (1.21,2.56)	
No qualification	731	36 (4.9)	695 (95.1)	1.82 (1.16,2.86)	
Occupation					<0.001
Manual worker	1088	74 (6.8)	1014 (93.2)	1	
Non-manual worker	1884	152 (8.1)	1732 (91.9)	0.83 (0.62,1.10)	
Never worked/retired	1805	73 (4.0)	1732 (96.0)	1.73 (1.24,2.41)	
Marital status					0.008
Married	4207	278 (6.6)	3929 (93.4)	1	
Single/divorced/widowed	570	21 (3.7)	549 (96.3)	1.85 (1.18,2.91)	
Residence					<0.001
Urban	2815	145 (5.2)	2670 (94.8)	1	
Rural	1962	154 (7.8)	1808 (92.2)	0.64 (0.50,0.81)	
Health insurance					<0.001
Yes	4211	232 (5.5)	3979 (94.5)	1	
No	564	67 (11.9)	497 (88.1)	0.43 (0.33,0.58)	
Smoking (current status)					0.073
No	3714	245 (6.6)	3469 (93.4)	1	
Yes	1063	54 (5.1)	1009 (94.9)	1.32 (0.98,1.79)	
Alcohol consumption (current status)					0.713
No	4169	263 (6.3)	3906 (93.7)	1	
Yes	608	36 (5.9)	572 (94.1)	1.07 (0.75,1.53)	
Duration of T2DM (years)					<0.001
≤1	981	93 (9.5)	888 (90.5)	1	
>1-5	880	60 (6.8)	820 (93.2)	1.43 (1.02,2.01)	
>5-10	1247	74 (5.9)	1173 (94.1)	1.66 (1.21,2.28)	
>10	1669	72 (4.3)	1597 (95.7)	2.32 (1.69,3.19)	
Blood glucose level (HbA1c)					0.458
<7%	899	64 (7.1)	835 (92.9)	1	

≥7%	3748	226 (6.0)	3522 (94.0)	1.19 (0.90,1.59)	
Unknown	130	9 (6.9)	121 (93.1)	1.03 (0.50,2.12)	

Table 3. Multiple backward stepwise logistic regression analysis for determining factors independently associated with comorbidity.

	Adjusted OR (95% CI)	P value
Age (years)		<0.001
18-39	1	
40-59	2.80 (1.98,3.96)	
60-69	4.43 (3.04,6.44)	
≥70	10.97 (7.17,16.77)	
Sex		<0.001
Male	1	
Female	0.66 (0.51,0.84)	
Marital status		0.006
Married	1	
Single/divorced/widowed	1.95 (1.21,3.12)	
Residence		0.018
Urban	1	
Rural	0.75 (0.59,0.95)	
Health insurance		0.002
Yes	1	
No	0.62 (0.46,0.83)	

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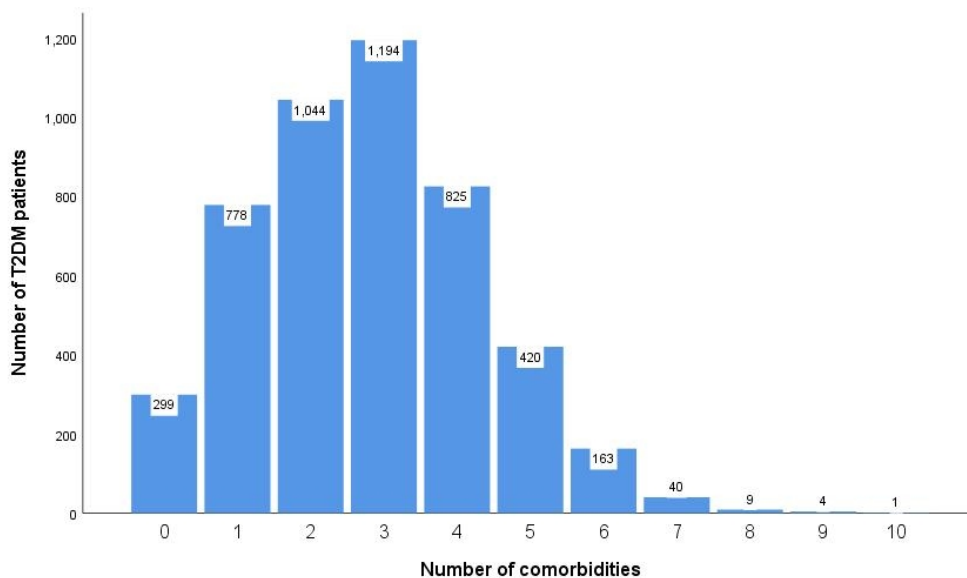


Figure 1. Number of comorbidities in our study.

300x176mm (72 x 72 DPI)

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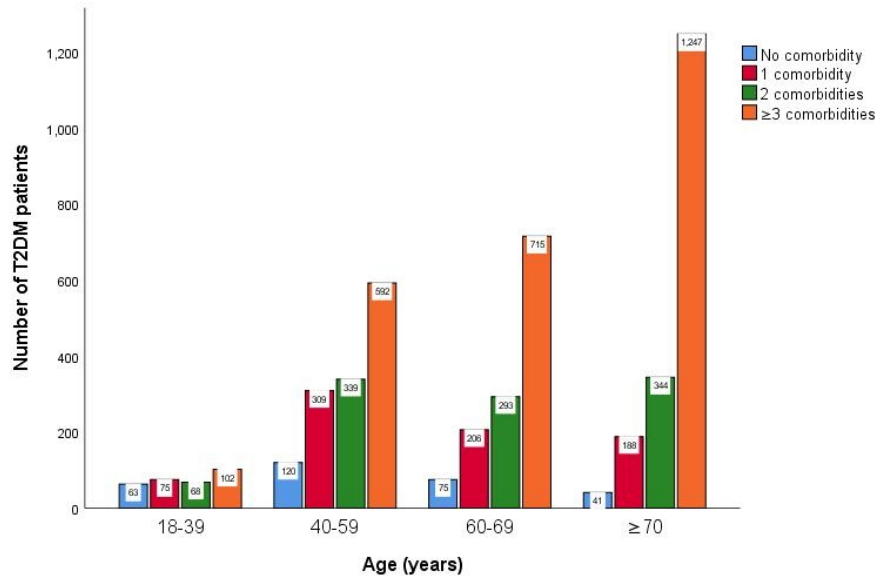


Figure 2. Number of comorbidities in our study in the different age groups.

300x176mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	7, Table2
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Table2
		(b) Indicate number of participants with missing data for each variable of interest	Table2
Outcome data	15*	Report numbers of outcome events or summary measures	7, Figure 1, Figure 2, Table1, Table2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8, Table2
		(b) Report category boundaries when continuous variables were categorized	7, 8, Table2, Table3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8, 9, 10, 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10, 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8, 9, 10, 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Prevalence of comorbidities and their associated factors in patients with type 2 diabetes at a tertiary care department in Ningbo, China: a cross-sectional study

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Title

Prevalence of comorbidities and their associated factors in patients with type 2 diabetes at a tertiary care department in Ningbo, China: a cross-sectional study

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Abstract

Objectives To determine the prevalence of comorbidities in patients with type 2 diabetes (T2DM) and identify the factors independently associated with comorbidities in a tertiary care department in Ningbo, China.

Design A computerised medical records database was used to conduct a cross-sectional study.

Setting The study was conducted in a tertiary care department in Ningbo, China.

Participants The study was conducted on adult patients with T2DM, and it included eight years of data, from 1 January 2012 to 31 December 2019.

The primary outcome measure Comorbidity was defined as the co-existence of at least one other chronic condition, i.e., either a physical non-communicable disease (duration ≥ 3 months), a mental health condition (duration ≥ 3 months), or an infectious disease (duration ≥ 3 months).

Results In total, 4777 patients with T2DM satisfied the eligibility criteria. Over eight years, the prevalence of comorbidities was 93.7%. The odds of comorbidities increased with the age of patients (18–39 years: 1; 40–59 years: odds ratio 2.80, 95% confidence interval 1.98–3.96; 60–69 years: 4.43, 3.04–6.44; and ≥ 70 years: 10.97, 7.17–16.77). The odds were lower in female patients (0.66, 0.51–0.84), patients residing in rural areas (0.75, 0.59–0.95), and patients without health insurance (0.62, 0.46–0.83). The odds were higher in single/divorced/widowed patients compared to those in married patients (1.95, 1.21–3.12).

Conclusions A large percentage of patients with T2DM in the tertiary care department in Ningbo, China, had comorbidities, and the factors associated with comorbidities were identified. The findings could be used in developing, evaluating, and

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4 implementing interventions aimed at improving outcomes in patients with T2DM with
5 comorbidities.
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8 **Keywords**

9 comorbidity, type 2 diabetes, China
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13 **Strengths and limitations of the study**

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- Ours was the first study to investigate comorbidities in patients with type 2 diabetes in Ningbo and the broader Zhejiang Province of China.
 - We included all the chronic conditions in our study; they were coded using the International Classification of Diseases, 10th edition (ICD-10) in our database.
 - Our study had extremely low missing data and the multiple logistic regression analysis included a sample with missing data for the adjusted variable.
 - As it was a cross-sectional study, the causal relationship between the variables and the comorbidities could not be determined.
 - The high prevalence of comorbidities in our study could be due to the study setting (i.e., hospital).

INTRODUCTION

Ningbo is an economically developed Chinese city in Zhejiang Province. The population of the city is approximately 8.2 million.[1] Non-communicable diseases are prevalent in the city, and one of the most prevalent non-communicable diseases is type 2 diabetes (T2DM), a complex metabolic disorder.[2] China has the largest T2DM epidemic in the world, and in Ningbo, its prevalence in adults ≥ 40 years of age is 21%.[3] In Ningbo, the diabetes-related mortality is 14.5 per 100,000 population.[4]

There is no international consensus regarding the best way to define comorbidity. It is usually defined as the co-existence of other conditions with an index condition (i.e., the main condition under study) where these other conditions are not consequences of the index condition.[5-7] Comorbidities accelerate the progression of individual conditions, encourage the development of other physical and mental conditions, and even lead to premature mortality.[8-10] Moreover, they negatively affect overall health, wellbeing, and functioning.[11, 12] Additionally, they lead to high treatment burden, high healthcare utilisation and expenditure, and loss of economic output.[13, 14] In real life, T2DM is rarely presented in isolation and is always accompanied by comorbidity.[15, 16]

To date, no study has been undertaken to investigate comorbidities in patients with T2DM in Ningbo. The study objectives were to determine the prevalence of comorbidities in patients with T2DM and identify the factors independently associated with comorbidities. This knowledge could be used in developing, evaluating, and implementing interventions aimed at improving outcomes in patients with T2DM with comorbidities.

METHODS

Study location, study design, data source, and study period

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4 We conducted the study in a tertiary care department, the Department of
5 Endocrinology and Metabolism, Ningbo First Hospital, in Ningbo, China. This tertiary
6 care hospital delivers speciality healthcare services, provides medical education, and
7 conducts research.[17,18] Locals and people from the surrounding areas visit this
8 hospital as no referral is required from the general practitioner.[17] An existing
9 computerised medical records database was used for conducting this cross-sectional
10 study. This database contained information on all inpatients. Since it was a real-time
11 database, new patients were added continuously. Data were entered by the medico-
12 nursing team and an independent group of the hospital staff was responsible for
13 assessing the quality of the data and overall database management. All the conditions
14 were coded using the International Classification of Diseases, 10th edition (ICD-10).
15 This retrospective study included eight years of data, from 1 January 2012 to 31
16 December 2019, and the information was available on 6755 patients.

31 **Study population and study inclusion and exclusion criteria**

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33 Adult patients (≥ 18 years) with T2DM were included. If a patient was admitted more
34 than once during the study period, data pertinent to the last admission were extracted
35 to obtain the most recent information on health conditions. Individuals with gestational
36 diabetes, type 1 diabetes, secondary diabetes, and unknown types of diabetes were
37 excluded.
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45 **Study variables**

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47 We extracted and categorised the following information from the database:
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- 49 • age (18–39 years, 40–59 years, 60–69 years or ≥ 70 years),
- 50 • sex (male or female),
- 51 • education (university/college, class 7–12, class 1–6, or no qualification),
- 52 • occupation (manual worker [i.e., more physical work than mental work], non-
53 manual worker [i.e., more mental work than physical work], or never
54 worked/retired),
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- marital status (married or single/divorced/widowed),
- residence (urban or rural using the “hukou” system i.e., the Chinese household registration system),
- health insurance,
- smoking (current status),
- alcohol consumption (current status),
- duration of T2DM (\leq 1 year, > 1–5 years, > 5–10 years, or > 10 years), and
- blood glucose level (glycated haemoglobin [HbA1c < 7% (good) or \geq 7% (poor)], estimated using the high-performance liquid chromatographic method and D-10 Haemoglobin Analyser [Bio-Rad, USA]). In China, the recommended HbA1c treatment target did not change over the study period (< 7% for most patients with T2DM).[19-21]

In addition, information on comorbidities was extracted. The index condition was T2DM. Comorbidity was defined as the co-existence of at least one other chronic condition, i.e., either a physical non-communicable disease (duration \geq 3 months), a mental health condition (duration \geq 3 months), or an infectious disease (duration \geq 3 months).[5-7] T2DM-specific complications (i.e., microvascular complications, such as diabetic retinopathy, nephropathy, and neuropathy/foot) were excluded as these were consequences of the index condition; hence, they were not considered as comorbidities.[6]

Ethics

The Research Ethics Committee of the Ningbo First Hospital, China, approved this study (2020-R106). The researchers had no access to information that could identify individual patients during the data analyses. No informed consent was required as per research ethics rules.

Patient and public involvement

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4 Patients and the public were not involved in the study.
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7 **Statistical analyses**

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9 We calculated numbers and percentages for categorical variables and means and
10 standard deviations (SDs) for normally distributed continuous variables. We used a
11 simple logistic regression method to investigate the association between the different
12 variables and comorbidities. We developed a multiple logistic regression model to
13 identify any independent associations. For this, we used backward stepwise
14 regression analysis and included all the variables. Additionally, we performed a
15 sensitivity analysis — in the multiple logistic regression model, we included only those
16 variables that had a p-value ≤ 0.20 in simple logistic regressions. We calculated odds
17 ratios (ORs) and 95% confidence intervals (CIs). We used IBM SPSS Statistics version
18 26.0 for Windows for statistical analyses.
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31 **RESULTS**

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33 A total of 4777 patients with T2DM satisfied the eligibility criteria. The mean (\pm SD) age
34 of patients was 64.2 (\pm 14.2) years, and approximately 52% (n=2482) of them were
35 men. The mean (\pm SD) HbA1c level was 9.2% (\pm 2.4%). Over eight years, the
36 prevalence of comorbidities was 93.7%. The year-wise prevalences from 2012 to 2019
37 were 96.9%, 95.0%, 92.9%, 95.5%, 93.2%, 91.5%, 94.0%, and 93.6%, respectively.
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45 Figure 1 shows the number of comorbidities in our study. The mean (\pm SD) number of
46 comorbidities was 3 (\pm 1). Figure 2 shows the percentage of comorbidities in our study
47 in the different age groups. In the ≥ 70 years age group, 68.5% (1247) had ≥ 3
48 comorbidities, whereas the prevalences were only 33.1% (102), 43.5% (592), and 55.5%
49 (715) in the 18–39, 40–59, and 60–69 years age groups, respectively. Table 1 reports
50 the most common comorbidities in our study. Essential hypertension (49.4%),
51 disorders of lipoprotein metabolism and other lipidaemias (33.7%), nontoxic thyroid
52 nodule (22.8%), fatty change of liver (20.6%), and cataract (10.7%) were the five most
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prevalent comorbidities.

Table 2 reports the characteristics of the study participants. We found that the comorbidities were associated with age, sex, education, occupation, marital status, residence, health insurance, and the duration of T2DM. Table 3 reports the multiple backward stepwise logistic regression analysis for determining factors independently associated with the comorbidities. The odds of comorbidities increased with the age of patients (18–39 years: 1; 40–59 years: OR 2.80, 95% CI 1.98–3.96; 60–69 years: 4.43, 3.04–6.44; and ≥ 70 years: 10.97, 7.17–16.77). The odds were lower in female patients (0.66, 0.51–0.84), patients residing in rural areas (0.75, 0.59–0.95), and patients without health insurance (0.62, 0.46–0.83). The odds were higher in single/divorced/widowed patients compared to married patients (1.95, 1.21–3.12). We obtained similar results in the sensitivity analysis.

DISCUSSION

In our tertiary care department in Ningbo, China, approximately 94% of the patients with T2DM had comorbidities and this influenced the overall management. In a previous study, we found that approximately 72% of the patients with T2DM were prescribed polypharmacy.[22] There are no similar studies on comorbidities conducted in patients with T2DM in China published in the English language. However, we found two similar studies published in Mandarin: one on patients with diabetes at a community health centre and another on outpatients with T2DM at a tertiary care hospital.[23, 24] The corresponding prevalence figures were around 95% and 73%, respectively. The different prevalence figures could be explained by the differences in population characteristics, the study setting, and the definition of comorbidity applied. Several studies have been conducted on this subject in high-income countries such as the United States and European countries.[25–29] All these studies, and also our study, have highlighted the fact that comorbidities are highly prevalent in patients with T2DM. A systematic review and meta-analysis of the prevalence of comorbidities in patients

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3 with T2DM in different geographical locations and the factors associated with it will be
4 helpful.
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9 Comorbidities are not synonymous with complications.[6] In a previous study on the
10 vascular complications of T2DM, we included microvascular complications (i.e.,
11 diabetic retinopathy, nephropathy, and neuropathy/foot) and macrovascular
12 complications (i.e., coronary heart disease, stroke, and peripheral arterial disease) and
13 found that more than half of the patients with T2DM had vascular complications.[30] In
14 the present study, we explored comorbidities in patients with T2DM using a
15 recommended definition. Comorbidity was defined as the co-existence of at least one
16 other chronic condition, either a physical (non-communicable/infectious disease) or
17 mental health condition.[5-7] Unlike the previous study, in the present study,
18 microvascular complications were excluded, as these were consequences of T2DM
19 and should not be considered as comorbidities.[6] Although human immunodeficiency
20 virus (HIV) infection, tuberculosis (TB) and mental health conditions are common
21 comorbidities in patients with T2DM,[31-34] these were not the most common
22 comorbidities in this study. The prevalences of these infectious diseases are low in
23 Ningbo,[35-38] and there are chances that mental health conditions were
24 underreported. It should also be noted that infectious diseases and mental health
25 conditions as index conditions are treated in other specialised hospitals in Ningbo.
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44 We found that the odds of comorbidities increased with age in patients with T2DM. Age
45 is one of the most well-studied and consistent determinants of comorbidities.[25, 28,39]
46 Age-related organ degeneration is a natural process and can lead to the development
47 of many health conditions.[40] However, it should be noted that comorbidities do not
48 correspond with age and they are not limited to the older population alone.[41] In our
49 study, the prevalences of comorbidities were around 80% and 91% in the 18–39 and
50 40–59 years age groups, respectively. We found that the odds of comorbidities were
51 lower in female patients with T2DM compared with those in their male counterparts.
52 This finding is consistent with other studies.[25, 28] This could be due to differences at
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4 the biological level. Another potential reason could be the reporting differences in sex-
5 specific health conditions. For example, female patients with T2DM often present with
6 atypical symptoms of cardiovascular diseases.[42] Additionally, the standard non-
7 invasive diagnostic tests perform better in men than in women.[43] All these hinder the
8 diagnosis of cardiovascular diseases in women. Another example is benign prostatic
9 hyperplasia, one of the most common comorbidities in our study. This comorbidity was
10 diagnosed because of the compulsory ultrasound scan of the urinary system of
11 patients with T2DM at our hospital for possible kidney diseases. In comparison, the
12 gynaecological examination is not a routine examination in women with T2DM.
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23 We found that the odds of comorbidities were lower in patients with T2DM residing in
24 rural areas compared to those in urban areas. This could be due to economic growth,
25 urbanisation, and its negative consequences such as an unhealthy lifestyle.[44-46]
26 The link between an unhealthy lifestyle and chronic conditions (particularly non-
27 communicable diseases) is well established.[47] A similar association has also
28 emerged with comorbidities.[23,48] Another reason could be that rural patients in
29 China have limited access to healthcare and thus, they may undergo fewer diagnostic
30 tests and obtain fewer confirmations of health conditions.[49] We found that the odds
31 of comorbidities were lower in patients with T2DM without health insurance compared
32 to those with health insurance. This could be due to the fact that over 90% of the
33 Chinese population have some sort of health insurance,[50] and these patients may
34 undergo more diagnostic tests (within the scope of their health insurance policy) and
35 obtain confirmation of a range of health conditions.[51] We found that the odds of
36 comorbidities were higher in single/divorced/widowed patients with T2DM compared
37 with those in married patients. In general, the spouses of married patients provide both
38 physical and mental support to them, and this could help them manage their existing
39 health conditions and prevent new ones from emerging.[52,53]
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58 This study has several strengths and weaknesses. Comorbidity is a less-explored area
59 in China, and to the best of our knowledge, this was the first study to explore
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4 comorbidities in patients with T2DM in Ningbo and the broader Zhejiang Province. The
5 quality of our routinely collected data was good. Unlike other studies where
6 comorbidities in T2DM were self-reported by the patients with T2DM using a
7 predetermined list of selected comorbidities,[23, 24] we used a holistic approach. All
8 the conditions were coded using the International Classification of Diseases, 10th
9 edition (ICD-10) in our database, and we included all the chronic conditions in our
10 study. This also minimised the possibility of recall bias in our study. Our study had
11 extremely low missing data; only HbA1c data were missing in 130 patients out of 4777
12 (i.e., 2.7%). Multiple logistic regression analysis included a sample with missing data
13 for the adjusted variable. Since it was a cross-sectional study, the causal relationship
14 between variables and comorbidities could not be determined. We propose to conduct
15 a longitudinal study to explore the effects of various factors on comorbidities, including
16 factors considered in this study and other factors such as physical activity and diet that
17 were not present in our database and could not be adjusted for in the models. In our
18 study, the high prevalence of comorbidities could be due to the study setting (i.e.,
19 hospital). The findings of our hospital-based study could be valid in similar settings.
20 We suggest conducting a population-based study that might provide a distinct picture
21 of the issue in Ningbo.
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41 In conclusion, we found that a large percentage of patients with T2DM in the tertiary
42 care department in Ningbo, China, had comorbidities, and we also identified the factors
43 associated with comorbidities. The findings could be used in developing, evaluating,
44 and implementing interventions aimed at improving outcomes in patients with T2DM
45 with comorbidities.
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53 management and organisation of the original data.
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58 **CONTRIBUTORS** JL and KC designed the study. XL and KC analysed the data and
59 wrote the first draft of the manuscript. SX and YC contributed to patient registration
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4 and data entry. XL contributed to data cleaning. XL, KC, SX, YC, MX, LL and JL revised
5 it critically for important intellectual content and approved the final version.
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17 **COMPETING INTERESTS** None declared.
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21 **ETHICS APPROVAL** The Research Ethics Committee of Ningbo First Hospital, China
22 approved the study (2020-R106).
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27 **DATA SHARING STATEMENT** The dataset will be available upon request unless
28 there are legal or ethical reasons for not doing so.
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Figure 1. Number of comorbidities in our study.

Figure 2. Percentage of comorbidities in our study in the different age groups.

Table 1. Most common comorbidities in our study.

Most common comorbidities (based on ICD-10 classification)	Patients with T2DM n (%)
Essential hypertension (I10)	2362 (49.4)
Disorders of lipoprotein metabolism and other lipidaemias (E78)	1612 (33.7)
Nontoxic thyroid nodule (E04)	1088 (22.8)
Fatty (change of) liver (K76)	984 (20.6)
Cataract (H26)	512 (10.7)
Chronic ischemic heart disease (I25)	455 (9.5)
Atherosclerosis (I70)	411 (8.6)
Osteoporosis (M81)	348 (7.3)
Cerebral infarction (I63)	341 (7.1)
Benign prostatic hyperplasia (N40)	303 (12.2*)
Abnormal findings on diagnostic imaging of lung (R91)	287 (6.0)
Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (M51)	260 (5.4)
Obesity (E66)	177 (3.7)
Cervical disc disorders (M50)	161 (3.4)
Chronic viral hepatitis (B18)	138 (2.9)
Sleep disorders (G47)	135 (2.8)
Gout (M10)	132 (2.8)
Disorders of purine and pyrimidine metabolism (E79)	127 (2.7)
Atrial fibrillation and flutter (I48)	118 (2.5)
Gastro-oesophageal reflux disease (K21)	111 (2.3)

*In 2482 males.

Table 2. Characteristics of the study participants.

	Total (4777)	Comorbidity No (299)	Comorbidity Yes (4478)	Unadjusted OR (95% CI)	P value

		n (%)	n (%)		
Age (years)					<0.001
18-39	308	63 (20.5)	245 (79.5)	1	
40-59	1360	120 (8.8)	1240 (91.2)	2.66 (1.90,3.71)	
60-69	1289	75 (5.8)	1214 (94.2)	4.16 (2.90,5.98)	
≥70	1820	41 (2.3)	1779 (97.7)	11.16 (7.37,16.90)	
Sex					0.008
Male	2482	133 (5.4)	2349 (94.6)	1	
Female	2295	166 (7.2)	2129 (92.8)	0.73 (0.57,0.92)	
Education					0.005
University/college	545	47 (8.6)	498 (91.4)	1	
Class 7-12	1927	136 (7.1)	1791 (92.9)	1.24 (0.88,1.76)	
Class 1-6	1574	80 (5.1)	1494 (94.9)	1.76 (1.21,2.56)	
No qualification	731	36 (4.9)	695 (95.1)	1.82 (1.16,2.86)	
Occupation					<0.001
Manual worker	1088	74 (6.8)	1014 (93.2)	1	
Non-manual worker	1884	152 (8.1)	1732 (91.9)	0.83 (0.62,1.10)	
Never worked/retired	1805	73 (4.0)	1732 (96.0)	1.73 (1.24,2.41)	
Marital status					0.008
Married	4207	278 (6.6)	3929 (93.4)	1	
Single/divorced/widowed	570	21 (3.7)	549 (96.3)	1.85 (1.18,2.91)	
Residence					<0.001
Urban	2815	145 (5.2)	2670 (94.8)	1	
Rural	1962	154 (7.8)	1808 (92.2)	0.64 (0.50,0.81)	
Health insurance					<0.001
Yes	4211	232 (5.5)	3979 (94.5)	1	
No	564	67 (11.9)	497 (88.1)	0.43 (0.33,0.58)	
Smoking (current status)					0.073
No	3714	245 (6.6)	3469 (93.4)	1	
Yes	1063	54 (5.1)	1009 (94.9)	1.32 (0.98,1.79)	
Alcohol consumption (current status)					0.713
No	4169	263 (6.3)	3906 (93.7)	1	
Yes	608	36 (5.9)	572 (94.1)	1.07 (0.75,1.53)	
Duration of T2DM (years)					<0.001
≤1	981	93 (9.5)	888 (90.5)	1	
>1-5	880	60 (6.8)	820 (93.2)	1.43 (1.02,2.01)	
>5-10	1247	74 (5.9)	1173 (94.1)	1.66 (1.21,2.28)	
>10	1669	72 (4.3)	1597 (95.7)	2.32 (1.69,3.19)	
Blood glucose level (HbA1c)					0.458
<7%	899	64 (7.1)	835 (92.9)	1	
≥7%	3748	226 (6.0)	3522 (94.0)	1.19 (0.90,1.59)	
Unknown	130	9 (6.9)	121 (93.1)	1.03 (0.50,2.12)	

Table 3. Multiple backward stepwise logistic regression analysis for determining factors independently associated with comorbidity.

	Adjusted OR (95% CI)	P value
Age (years)		<0.001
18-39	1	
40-59	2.80 (1.98,3.96)	
60-69	4.43 (3.04,6.44)	
≥70	10.97 (7.17,16.77)	
Sex		<0.001
Male	1	
Female	0.66 (0.51,0.84)	
Marital status		0.006
Married	1	
Single/divorced/widowed	1.95 (1.21,3.12)	
Residence		0.018
Urban	1	
Rural	0.75 (0.59,0.95)	
Health insurance		0.002
Yes	1	
No	0.62 (0.46,0.83)	

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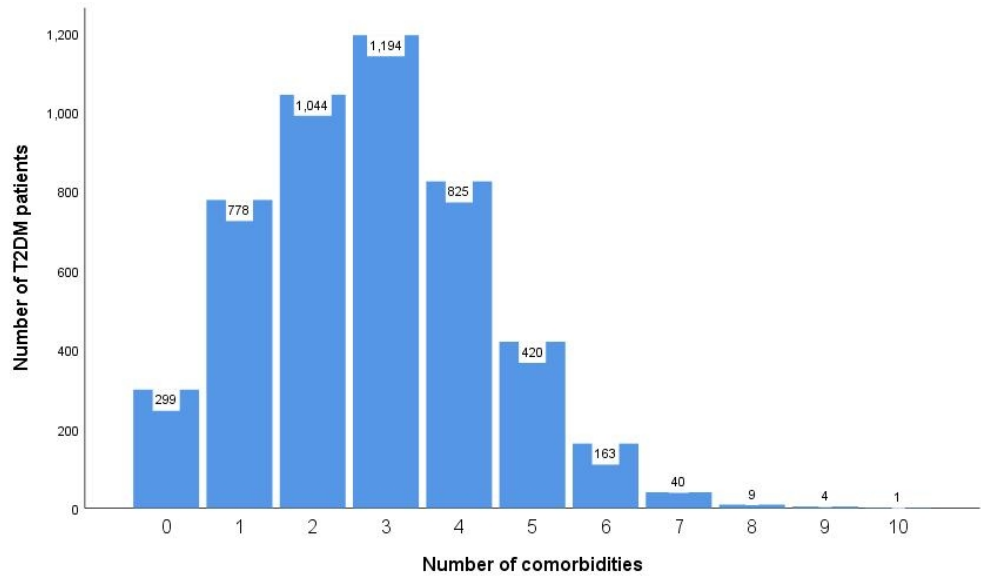


Figure 1. Number of comorbidities in our study.

300x176mm (72 x 72 DPI)

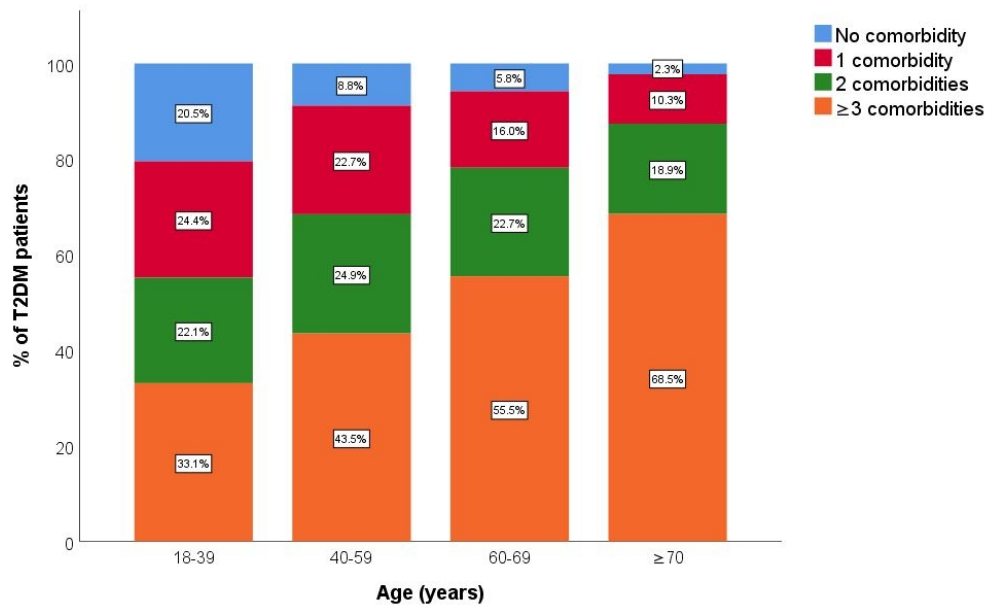


Figure 2. Percentage of comorbidities in our study in the different age groups

256x159mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6,7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	7, Table2
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, Table2
		(b) Indicate number of participants with missing data for each variable of interest	Table2
Outcome data	15*	Report numbers of outcome events or summary measures	7, Figure 1, Figure 2, Table1, Table2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, 8, Table2
		(b) Report category boundaries when continuous variables were categorized	7, 8, Table2, Table3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8, 9, 10, 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10, 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8, 9, 10, 11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.