



Association between diabetes and acute lymphocytic leukemia, acute myeloid leukemia, non-Hopkin lymphoma, and multiple myeloma

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Abstract

Objective Diabetes increases the risk for cancers. However, whether it is associated with hematologic malignancies is not clear. The present study investigated the association between diabetes and acute lymphocytic leukemia (ALL), acute myeloid leukemia (ML), non-Hopkin lymphoma (NHL), and multiple myeloma (MM).

Methods Newly diagnosed adult cancer patients were recruited consecutively from our clinical database. Peoples from a local enterprise were recruited to create a small-scale population-based dataset. We compared the diabetes prevalence between the cancer patients and the local people; an increase in diabetes prevalence in the cancer patients suggests an association between diabetes and the cancer(s).

Results We found that the prevalence of diabetes was 19.7%, 21.3%, 12.5%, and 12.0% in ALL, AML, NHL, and MM, respectively, which was higher than that (9.1%) in the local people. Despite that there were more male than female cancer patients, there were more female than male diabetic patients. The increase in diabetes prevalence occurred in ALL and NHL patients aged 18 to 39 years old as well as in AML patients over 40. In MM patients, the increase in diabetes prevalence (18.6%) occurred only in females. Approximately 70% of the diabetic patients were undiagnosed before the diagnosis of the blood cancer. Approximately half of the pre-existing diabetic patients had anti-diabetic treatment, with over 70% of them still had poor glycemic control.

Conclusions Our results suggest that diabetes is associated with ALL, AML, NHL, and MM, at least in adult patients.

Keywords Diabetes · Acute lymphocytic leukemia · Acute myeloid leukemia · Non-Hopkin lymphoma · Multiple myeloma · Association

Introduction

Both diabetes and cancer are common non-communicable diseases with increasing prevalence. According to the Global Report on Diabetes from the World Health Organization, the prevalence of diabetes has increased from 4.7% in 1980 to 8.5% in 2014, with 422 million adults diagnosed with the disease. It is estimated that 451 million adults had diabetes in 2017, with almost half of all people living with undiagnosed diabetes [1]. Cancer is the second leading cause of death world-wide. According the statistics from the World Health Organization, cancer caused approximately 9.6 million deaths, or one in six deaths, in 2018 [2]. Diabetes and cancer cast enormous socioeconomic burden to societies. More 60 years ago, concurrent diabetes and cancer in patients had already been noted in clinical setting. However, it remained inconclusive of whether the two diseases are associated until recent decades when diabetes and cancer are highly

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prevalent. In the past decades, epidemiological studies showed that diabetes was associated with the occurrence of various cancers such as those in the liver, pancreas, stomach, colorectum, kidney, and breast. It is postulated that the pre-diabetic and diabetic states increase the risk for cancer. However, those presented results were not clear and sometimes conflicting [3]. In relevance to hematologic cancers, more recently, Castillo and co-workers performed a meta-analysis based on 13 case–control and 13 cohort studies, and found that diabetes was associated with NHL ($p < 0.01$), leukemia ($p = 0.02$), and possibly myeloma ($p = 0.08$) [4]. Yan et al. reported that type 2 rather than type 1 diabetes is associated with leukemia [5]. In a large insurance database in Taiwan, diabetes was found to be associated with NHL in both male and female groups [6]. Analysis on databases from Shanghai also revealed that patients with diabetes had an increased risk for NHL [7]. Wang et al. performed a meta-analysis on 35 cohort studies, and found a moderate increase in risk of NHL in types 1 and 2 diabetes, which was more significant in Asians [8]. Data from another meta-analysis supported the view that diabetes increases the risk for NHL, and further pointed out that male diabetic patients were more likely to develop NHL than females [9]. However, there are studies which showed that diabetes does not increase the overall risk for blood cancer, even in large database [10]. Diabetes might not only modify the cancer risk but also the cancer course. Indeed, diabetes and pre-diabetic state are associated with poorer prognosis of chronic lymphocytic leukemia [11], NHL [12], and myeloma [13]. On the other hand, anti-diabetic treatment, in particular by metformin, not only reduces the risk for lymphoma [14] but also improves the prognosis of lymphoma [15] and myeloma [16]. Although it is possible that metformin reduces cancer risk in diabetes by improving the metabolic profile, it has been shown to directly act on cancer cells. The compound inhibits in vitro cancer cell proliferation, migration, and invasion as well as induces apoptosis and autophagy [17], which inhibits the tumorigenesis and tumor progression [18]. In relevance to leukemia, some believed that metformin could be used to treat leukemia [19]. However, there was also evidence that metformin had neutral effect on leukemia, and yet, there was possibility that long-term use of the drug might increase the cancer risk [20].

The published meta-analyses were performed on limited number of original studies completed in different time and geographic location. The heterogeneity may affect the analysis outcome, as differences in genetic composition and life style may produce biases [4]. Anti-diabetic drugs, in particular metformin, are found to modify cancer risk, thus, including study before and after the common use of metformin in meta-analysis may produce bias. Moreover, hematologic cancers are heterogeneous and inclusion of acute lymphocytic or myeloid leukemia in analysis, rather only leukemia,

might provide more informative insights. Thus, more original studies are required for a better view on the relationship between diabetes and hematologic malignancies. The present study examined the prevalence of diabetes in newly diagnosed adult patients with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), NHL, or multiple myeloma (MM) to assess the association between diabetes and the blood malignancies. The subjects were recruited from our region and the influence of the use of metformin was minimized, which was believed to avoid the biases which might be produced by the current meta-analyses.

Research design and methods

Approval for the study was obtained from the Clinical Ethics Committee of Linyi People's Hospital which is the major regional hospital with a catchment population of 1.29 million with typical demographic and social class distributions. Most of the inhabitants are eastern Chinese in origin. Because of the lack of a long-term health care financing policy, the majority of people in this region do not have medical insurance for chronic diseases, such as cancer and diabetes. As a result, most of these patients seek medical care at the public hospitals where only nominal fees are charged. The cancer patients aged from 18 years or above, who were hospitalized between 2015 and 2020, were consecutively recruited. We recruited 1050 local people to create a small-scale population-based survey dataset in 2019.

AML, ALL, and NHL were diagnosed and classified according to the 2016 WHO criteria [21, 22]. MM was diagnosed and classified according to the criteria by the 2014 International Myeloma Working Group [23]. Fasting blood samples were taken for biochemical assays. For the cancer patients, blood samples were taken on the diagnosis of cancer before any clinical treatment. Diabetes was evidenced when fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) [24]. Those with diabetes history were also included in the diabetes group, even though they had achieved satisfactory glycemic control. In the study, the patients with AML, ALL, NHL, and MM were 622, 416, 789, and 392, respectively. The subjects randomly recruited outside the hospital for the estimation of diabetes prevalence were 1052. Soon after admission of the patients, fasting blood samples were taken to the biochemical analyses. For the subjects recruited from outside the hospital, who were involved in the survey for the estimation of diabetes prevalence, fasting blood samples were taken for the determination of the metabolic profile.

Fasting blood glucose levels were measured using a hexokinase method. Plasma levels of total cholesterol and triglyceride were assayed enzymatically using commercially available reagents (Beckmancoulter; Beckman Instrument, USA). HDL-cholesterol was detected using the selective

Table 1 Demographic data of the adult patients with ALL, AML, NHL, or MM

Cancer type	Clinical parameter	Adult patients with ALL, AML, NHL, or MM				
		Overall (<i>n</i> = 2219)	Men (<i>n</i> = 1266)	Women (<i>n</i> = 911)	Non-diabetic	Diabetic
AML	Age (95% CI)	51.71 (50.48 to 52.93)	52.43 (50.75 to 54.12)	50.89 (49.11 to 52.66)	50.39 (48.98 to 51.81)	57.23 (55.00 to 59.47)***
	Fasting plasma glucose (mmol/L) (95% CI)	6.33 (6.15 to 6.51)	6.26 (6.01 to 6.51)	6.40 (6.14 to 6.67)	5.52 (5.45 to 5.58)	9.63 (9.04 to 10.22)***
	Total cholesterol (mmol/L) (95% CI)	3.71 (3.60 to 3.82)	3.57 (3.43 to 3.72)	3.88 (3.71 to 4.05)*	3.73 (3.60 to 3.85)	3.63 (3.37 to 3.89)
	Low-density lipoprotein (mmol/L) (95% CI)	2.31 (2.23 to 2.40)	2.23 (2.12 to 2.34)	2.42 (2.29 to 2.55)*	2.32 (2.23 to 2.42)	2.26 (2.06 to 2.46)
	High-density lipoprotein (mmol/L) (95% CI)	0.89 (0.86 to 0.92)	0.86 (0.83 to 0.90)	0.93 (0.87 to 0.97)*	0.91 (0.86 to 0.94)	0.83 (0.78 to 0.88)
	Triglycerides (mmol/L) (95% CI)	1.51 (1.41 to 1.61)	1.40 (1.29 to 1.52)	1.65 (1.48 to 1.82)*	1.50 (1.39 to 1.62)	1.57 (1.38 to 1.76)
ALL	Age (95% CI)	41.98 (38.99 to 44.97)	43.29 (38.96 to 47.62)	40.38 (36.22 to 44.54)	41.00 (37.82 to 44.18)	47.57 (38.19 to 56.95)
	Fasting plasma glucose (mmol/L) (95% CI)	5.70 (5.34 to 6.01)	5.82 (5.29 to 6.35)	5.56 (5.06 to 6.06)	5.11 (4.94 to 5.27)	9.28 (8.04 to 10.52)***
	Total cholesterol (mmol/L) (95% CI)	4.08 (3.77 to 4.39)	4.14 (3.72 to 4.56)	4.02 (3.54 to 4.50)	4.08 (3.73 to 4.44)	4.13 (3.28 to 4.98)
	Low-density lipoprotein (mmol/L) (95% CI)	2.60 (2.36 to 2.84)	2.67 (2.38 to 2.96)	2.54 (2.16 to 2.92)	2.59 (2.32 to 2.86)	2.74 (2.11 to 3.37)
	High-density lipoprotein (mmol/L) (95% CI)	0.88 (0.80 to 0.96)	0.84 (0.72 to 0.96)	0.91 (0.81 to 1.02)	0.90 (0.81 to 0.99)	0.81 (0.59 to 1.03)
	Triglycerides (mmol/L) (95% CI)	1.92 (1.40 to 2.43)	1.66 (1.5 to 1.8)	1.74 (1.53 to 1.93)	1.66 (1.52 to 1.80)	1.83 (1.52 to 2.14)
NHL	Age (95% CI)	57.63 (56.22 to 59.03)	57.56 (55.78 to 59.35)	57.73 (55.43 to 60.04)	57.43 (55.88 to 58.98)	58.84 (55.58 to 62.1)
	Fasting plasma glucose (mmol/L) (95% CI)	5.71 (5.53 to 5.88)	5.64 (5.43 to 5.84)	5.83 (5.51 to 6.16)	5.15 (5.08 to 5.23)	9.13 (8.46 to 9.80)***
	Total cholesterol (mmol/L) (95% CI)	4.16 (4.00 to 4.34)	3.99 (3.78 to 4.20)	4.50 (4.25 to 4.75)*	4.21 (4.04 to 4.39)	3.74 (3.25 to 4.23)
	Low-density lipoprotein (mmol/L) (95% CI)	2.69 (2.58 to 2.80)	2.62 (2.48 to 2.76)	2.82 (2.64 to 3.00)	2.71 (2.60 to 2.83)	2.49 (2.17 to 2.81)
	High-density lipoprotein (mmol/L) (95% CI)	1.11 (1.04 to 1.18)	1.11 (1.01 to 1.21)	1.10 (1.01 to 1.20)	1.14 (1.06 to 1.22)	0.83 (0.73 to 0.93)*
	Triglycerides (mmol/L) (95% CI)	1.40 (1.28 to 1.52)	1.44 (1.27 to 1.60)	1.33 (1.17 to 1.49)	1.41 (1.28 to 1.54)	1.30 (1.00 to 1.61)

Table 1 (continued)

Cancer type	Clinical parameter	Adult patients with ALL, AML, NHL, or MM				
		Overall (n = 2219)	Men (n = 1266)	Women (n = 911)	Non-diabetic	Diabetic
MM	Age (95% CI)	61.69 (60.73 to 62.65)	61.24 (59.91 to 62.57)	62.34 (60.97 to 63.7)	61.75 (60.7 to 62.8)	61.28 (58.92 to 63.63)
	Fasting plasma glucose (mmol/L) (95% CI)	5.77 (5.57 to 5.97)	5.79 (5.50 to 6.07)	5.74 (5.47 to 6.01)	5.25 (5.18 to 5.33)	9.54 (8.46 to 10.63)***
	Total cholesterol (mmol/L) (95% CI)	3.82 (3.63 to 4.01)	3.62 (3.41 to 3.84)	4.12 (3.76 to 4.45)*	3.84 (3.63 to 4.04)	3.71 (3.20 to 4.21)
	Low-density lipoprotein (mmol/L) (95% CI)	2.34 (2.19 to 2.49)	2.20 (2.03 to 2.36)	2.55 (2.28 to 2.81)*	2.35 (2.19 to 2.51)	2.24 (1.88 to 2.61)
	High-density lipoprotein (mmol/L) (95% CI)	0.96 (0.92 to 1.01)	0.94 (0.88 to 1.00)	0.99 (0.93 to 1.06)	0.97 (0.92 to 1.01)	0.90 (0.74 to 1.06)
	Triglycerides (mmol/L) (95% CI)	1.40 (1.28 to 1.51)	1.32 (1.16 to 1.47)	1.51 (1.33 to 1.69)	1.35 (1.24 to 1.47)	1.74 (1.20 to 2.27)*

Data are expressed in mean (95% confidence interval)

* $p < 0.05$; *** $p < 0.001$, compared between males and females or diabetic and non-diabetic patients

inhibition method. LDL-cholesterol was measured using a surfactant method. All biochemical variables were measured using an autoanalyzer (Beckmancoulter AU5821; Beckman Instrument, USA) at the biochemical laboratory of the Linyi People's Hospital. Fasting blood samples were centrifuged (3000 rpm, 10 min) to obtain serum fraction. Exactly 1.2- μ l serum was loaded onto the automatic analyzing machine each time, separately, for the quantification of glucose, HDL-C, LDL-C, and total cholesterol, using the primary and secondary wavelengths at 340 nm and 660 nm, 600 nm and 700 nm, and 540 nm and 600 nm, respectively. Exactly 1.6- μ l serum was loaded to determine the level of triglyceride at the primary and secondary wavelengths at 660 and 800 respectively.

All data for continuous variables are expressed as mean (95% confidence interval) and were assessed using Student's *t*-test. χ^2 test was performed for analyzing proportions. The statistical analyses were performed using the Statistical Package for Social Sciences version 26 (SPSS, Chicago). A *p* value < 0.05 was considered to be statistically significant. We also confirmed all methods were performed in accordance with the relevant guidelines and regulations.

Results

Table 1 shows the clinical data of the patients with ALL, AML, NHL, or MM. The prevalence of diabetes was 19.7%, 21.3%, 12.5%, and 12.0% in ALL, AML, NHL, and MM

patients, respectively (Table 2; Fig. 1), which was higher than that (9.1%) in our local people and that (8.7% and 9.7%) in two recent national surveys (Table 3; Fig. 2). As shown in Table 2 and Fig. 1, there were more male than female patients in all the four cancer groups, with the male to female ratio of 1.24:1, 1.13:1, 1.74:1, and 1.43:1 in the ALL, AML, NHL, and MM patients, respectively. In contrast, the prevalence of diabetes was higher in the female than male cancer patients, although the difference did not reach a statistically significant level upon our sample size. Moreover, the increase in diabetes prevalence occurred in ALL and NHL patients aged 18 to 39 years old, and in AML patients aged over 40. In MM patients, the increase in diabetes prevalence (18.6%) occurred in female patients, rather than in a specific age group. In the cancer patients, approximately 70% of the diabetes cases were undiagnosed before the diagnosis of the cancer. Approximately half of the pre-existing diabetic patients had anti-diabetic treatment, with over 70% of them still had poor glycemic control.

Discussion

AML is the most common leukemia in adults, with more male than female patients [26], which accounts for around 1.3% of all new cancer cases in the USA in 2015 [27]. The development of ALL shows a bi-model feature, with one peak at children and the other at around 50 years old. In a Chinese population, the incidence of ALL was 0.63 per

Table 2 Prevalence of diabetes in the patients with ALL, AML, NHL, or MM

	ALL			AML			NHL			MM							
	<i>n</i>	Self-reported (%)	FPG \geq 7 (%)	Self-reported or FPG \geq 7 (%)	<i>n</i>	Self-reported (%)	FPG \geq 7 (%)	Self-reported or FPG \geq 7 (%)	<i>n</i>	Self-reported (%)	FPG \geq 7 (%)	Self-reported or FPG \geq 7 (%)					
Total	416	5.3 (3.15 to 7.45)	18.7 (14.95 to 22.45)	19.7 (15.9 to 23.5)***	622	6.4 (4.5 to 8.3)	19.7 (16.6 to 22.8)	21.3 (18.1 to 24.5)***	789	3.4 (2.1 to 4.7)	11.4 (9.2 to 13.6)	12.5 (10.2 to 14.8)**	392	4.3 (2.3 to 6.3)	12.0 (8.8 to 15.2)	14.3 (10.8 to 17.8)**	
Men	229	4.4 (1.74 to 7.06)	17.5 (12.58 to 22.42)	18.3 (13.3 to 23.3)**	330	5.2 (2.8 to 7.6)	17.5 (13.4 to 21.6)	19.4 (15.1 to 23.7)***	476	3.8 (2.1 to 5.5)	10.2 (7.5 to 12.9)	11.1 (8.3 to 13.9)	231	2.6 (0.5 to 4.7)	10.0 (6.1 to 13.9)	11.7 (7.6 to 15.8)	
Women	184	6.5 (2.94 to 10.06)	20.6 (14.76 to 26.44)	21.7 (15.7 to 27.7)***	292	7.9 (4.8 to 11.0)	21.9 (17.2 to 26.6)	23.6 (18.7 to 28.5)***	274	3.3 (2.1 to 5.4)	12.9 (8.9 to 12.9)	13.9 (9.8 to 18.0)**	161	6.8 (2.9 to 10.7)	14.9 (9.4 to 20.4)	18.6 (12.6 to 24.6)***	
Age	18–39	124	1.6 (0.08 to 3.16)	12.9 (7.00 to 18.8)	13.7 (7.7 to 19.8)***	143	—	5.6 (1.8 to 9.4)	5.6 (1.8 to 9.4)	100	3.0 (0.1 to 6.0)	7.0 (2.0 to 12.0)	7.0 (2.0 to 12.0)*	7	—	—	—
	40–59	110	3.6 (0.12 to 7.08)	18.2 (10.99 to 25.41)	19.1 (11.8 to 26.5)*	255	7.5 (4.3 to 10.7)	21.6 (16.5 to 26.7)	23.1 (17.9 to 28.3)***	293	2.0 (0.4 to 3.6)	10.9 (7.3 to 14.5)	11.6 (7.9 to 15.3)	153	3.3 (0.5 to 6.1)	11.8 (6.7 to 16.9)	12.4 (7.2 to 17.6)
	> 60	173	9.2 (4.89 to 13.51)	23.7 (17.4 to 30.0)	24.9 (18.5 to 31.3)	224	9.4 (5.6 to 13.2)	26.3 (20.5 to 32.1)	29.5 (23.5 to 35.5)*	357	5 (2.7 to 7.3)	14.3 (10.7 to 17.9)	16.2 (12.4 to 20.0)	232	5.2 (2.3 to 8.1)	12.5 (8.2 to 16.8)	15.9 (11.2 to 20.6)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, compared with the prevalence of diabetes in local people (Table 3)

FPG fasting plasma glucose

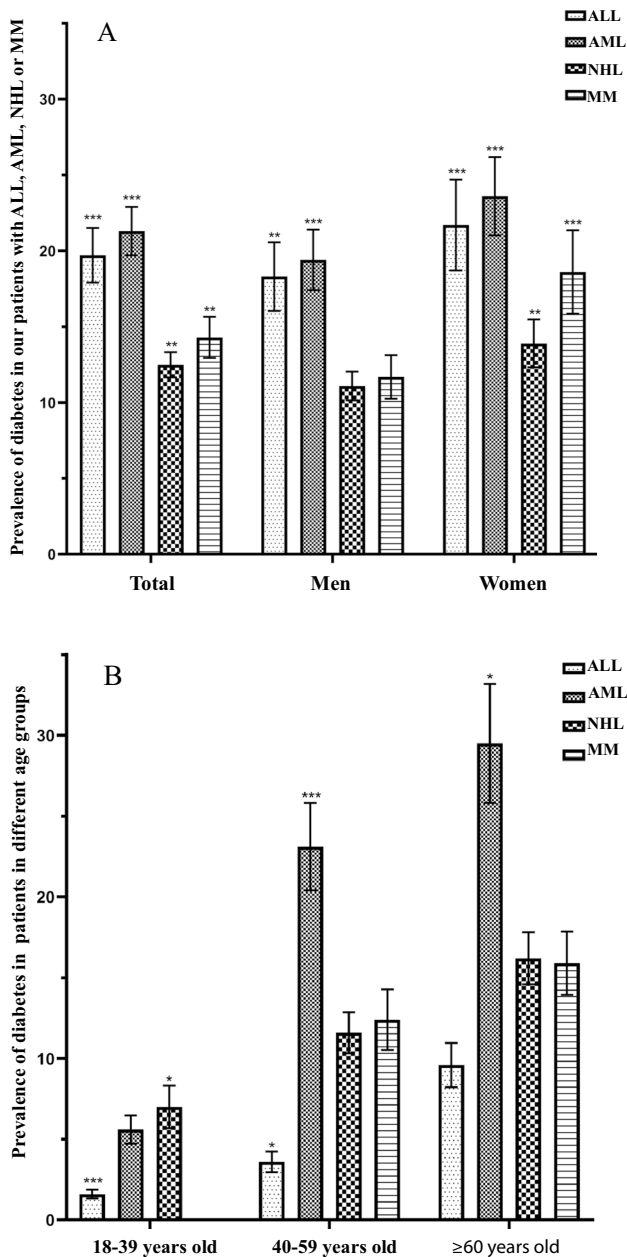


Fig. 1 Prevalence of diabetes in our adult patients with ALL, AML, NHL, or MM. **A** The prevalence of diabetes in all patients as well as male and female patients. **B** The prevalence of diabetes in our patients according to different age groups. * $p < 0.05$, *** $p < 0.001$, compare to the prevalence of diabetes in our survey in our local population and those reported in two national surveys (Fig. 2). The diagnosis criteria of diabetes used in our study and the national surveys are the same

100,000 people, with the male:female ratio of approximately 1.5:1 [28]. Although AML in adults is less common compared with ALL, it represents a devastating clinical condition. The increase in prevalence and improved therapy

Table 3 Prevalence of diabetes in population-based subjects

	Local population-based subjects		Published national surveys		
	n	Self-reported (%)	Self-reported or FPG ≥ 7 mmol/L (%)	Survey 1 [24]	Survey 2 [25]
Total	1052	2.7 (1.7 to 3.7)	9.1 (7.4 to 10.8)	8.7	9.7
Men	601	3.5 (2.0 to 5.0)	11 (8.5 to 13.5)	9.7	10.6
Women	451	1.6 (0.4 to 2.8)	6.7 (4.4 to 9.0)	7.7	8.8
Age	18–39	0.9 (0 to 1.8)	2.5 (1.1 to 3.9)	2.6	3.2
	40–59	4.3 (2.3 to 6.3)	10.4 (7.5 to 13.3)	11.1	11.5
	> 60	6.9 (3.3 to 10.5)	20.2 (14.5 to 25.9)	20.4	20.4

Date are expressed in prevalence (95% confidence interval) or prevalence alone

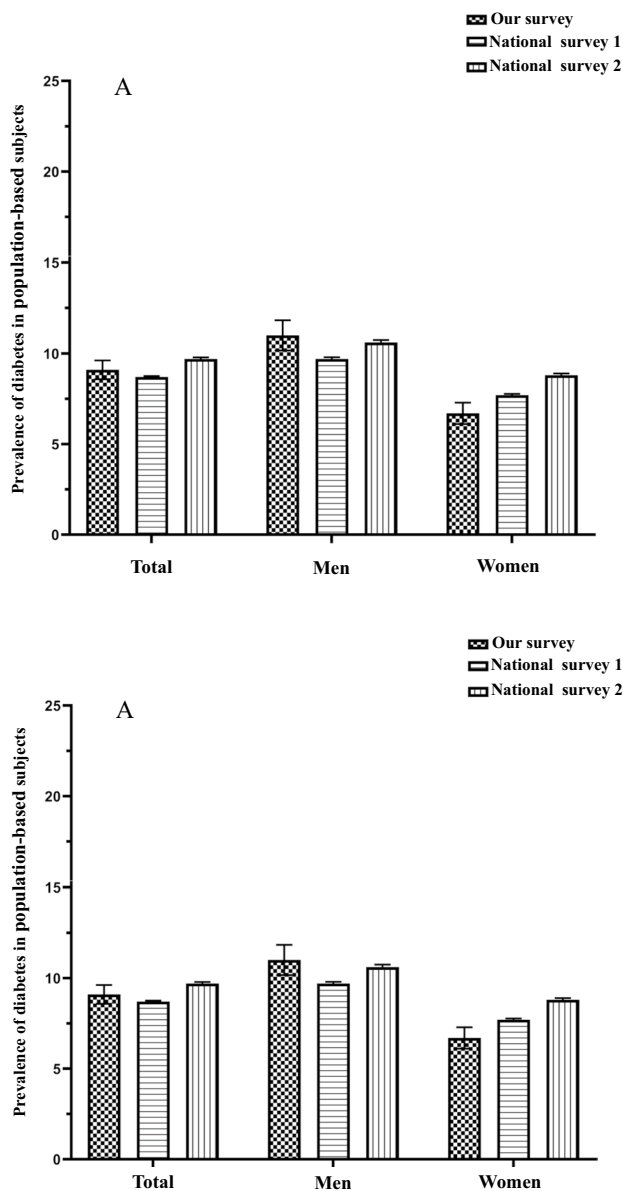


Fig. 2 The prevalence of diabetes in our local population and in national surveys. **A** The prevalence of diabetes in our local population and those reported in the two national surveys. **B** The prevalence of diabetes in our local population and reported in a national survey according to the age groups. There was no significant difference in the prevalence of diabetes between our local population and the population recruited for the national surveys. The numbers of male and female subjects were available from the national survey 1 but not 2; thus, only the data of diabetes prevalence of diabetes in different age groups from the national survey 1 were shown and used in the statistical analysis

outcome has increased the number of patients with NHL. From a population-based database in Taiwan, the incidence of MM is estimated to be 1.83 per 100,000 people, with more male than female patients [29]. Despite that diabetes is now known to increase the risk for various cancers, whether

the metabolic disease is associated with these hematologic malignancies still remains inconclusive. Our results showed that diabetes prevalence was increased in all of the patients with ALL, AML, NHL, or MM, suggesting that diabetes is associated with the four hematologic malignancies, in particular ALL and AML. In our study, most diabetes cases were undiagnosed before the diagnosis of the blood cancer, and majority of the patients with diabetes history had poor glycemic control, which indicates that our results are not confounded by anti-diabetic treatment, but may truly reflect the impact of metabolic disorder on the risk for the blood cancers. The people living with undiagnosed diabetes are at serious risk for developing cancer, including the hematologic malignancies.

Similar to the previous observations in the literature, we found that there were more male than female patients with the blood cancers, suggesting an increased susceptibility to the blood cancers in males. In contrast, in the ALL, AML, NHL, and MM patients, there were more female than male diabetic patients, although the difference did not reach a statistically significant level upon the sample size. However, the female:male ratio in the diabetic patients was significantly increased compared to that in the non-diabetic cancer patients ($p=0.004$), if patients with ALL, AML, NHL, or MM were combined. In a report on pancreatic cancer, the authors showed that the number of female diabetic patients was significantly higher than that of diabetic males ($p=0.008$) [30]. Thus, the association of diabetes with cancer might have a female preponderance.

Commonly, researchers analyze cancer prevalence in diabetes to assess the impact of diabetes on cancer risk. In the present study, we analyzed the diabetes prevalence in cancer patients to reflect the disease association. Such strategy, although uncommon, did have been employed by investigators [30], which can also produce informative data. There are possible biases in our analysis. Firstly, the sample size is limited, which may not be adequate for revealing the disease association correctly, and may be able for fully documenting the characters of the association (i.e., female preponderance).

Whether and how diabetes promotes cancer development remains unknown. Overweight and lifestyle were both confounding factors, and high glucose and insulin use were speculated to favor tumorigenesis via various mechanisms. TET2, a tumor suppressor which can repress leukemia progression, is a substrate of the AMP-activated kinase (AMPK) which phosphorylates TET2 at serine 99 and thereby stabilizes it for tumor repression. However, in the case of diabetes, increased glucose level impedes AMPK-mediated phosphorylation at serine 99, which results in the destabilization and degradation of TET2, which links diabetes to cancer [31]. In genetically modified experimental models, centrosome amplification is sufficient to cause tumorigenesis.

It would be interesting to investigate whether centrosome amplification is a biological link between diabetes and blood malignancies, since centrosome amplification occurs in cells with centrosome amplification can form tumors in recipient animals and mice spontaneously develop tumors, suggesting that centrosome amplification can cause tumorigenesis. Centrosome amplification occurs in myelodysplastic syndromes [32], leukemia [33], lymphoma [34], and myeloma [35]. Diabetes lowers the level of leukemia inhibitory factor that can induce differentiation and inhibits proliferation of leukemic cells [36, 37], which is also candidate mechanism. Alternatively, the association between diabetes and leukemia might reflect their shared etiological mechanisms rather than a promoting effect of diabetes on tumorigenesis. Let-7 is a family of non-coding microRNAs that include Let-7a to g, Let-7i, and miR-98. In leukemia, several let-7 family members (let-7a to f) were upregulated and associated with a high grade of the cancer [38, 39]. On the other hand, let-7 can act as an essential factor to regulate glucose metabolism [40]. Lin28/let-7 is a self-renewal system [41], in which let-7 is inhibited by Lin28. In muscle cells, both Lin28a knock-down or let-7 over-expression result in insulin resistance and impaired glucose [40]. Thus, Let-7 might be a common etiological factor for diabetes and leukemia.

Conclusion

Our results showed that many diabetic patients remained undiagnosed with poor glycemic profile. Diabetes was over presented in patients with ALL, AML, NHL, and MM, which was more obvious in the female than that in the male cancer patients. It is suggested that diabetes increases the risk for these hematologic cancers in adults, in particular in the females.

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Author contribution J.Z. Zhao, Y.C. Lu, Y.M. Wang, B.L. Xiao, and H.Y. Li collected the data. J.Z. Zhao and Y.C. Lu prepared Tables 1, 2, and 3. S.C. Lee and L.J. Wang applied for research grants, designed the study, interpreted the data, and wrote the manuscript. All authors reviewed the manuscript.

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Data availability The data are available from the corresponding authors.

Declarations

Statement of ethics Approval for the study was obtained from the Clinical Ethics Committee of Linyi People's Hospital. This research is strictly complying with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All of the patients and their guardians have given their written informed consent.

Conflict of interest The authors declare no competing interests.

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