Mediterranean Journal of
Pharmacy & Pharmaceutical Sciences
www.medjpps.com

ISSN: 2789-1895 online
ISSN: 2958-3101 print

ORIGINAL RESEARCH article

Knowledge of metformin-induced vitamin B-12 deficiency and its association with Alzheimer's disease among medical graduates

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Article number: 236, **Received:** 28-10-2025, **Accepted:** 06-01-2026, **Published online:** 11-01-2026

HOW TO CITE THIS

Ibraheim et al. Knowledge of metformin-induced vitamin B-12 deficiency and its association with Alzheimer's disease among medical graduates. Mediterr J Pharm Pharm Sci. 2026; 6(1): 11-20. [Article number: 236].
https://doi.org/10.5281/zenodo.18176820

Keywords: Libya, medical graduates, pharmacy graduates, type 2 diabetes mellitus

Abstract: Metformin is commonly prescribed as first-line therapy for type 2 diabetes mellitus. Despite its clinical benefit. long-term use has been associated with vitamin B-12 deficiency, which can lead to neurological dysfunction and cognitive disorders, including Alzheimer's disease. Awareness of this drug-nutrient interaction among healthcare professionals is essential for safe and effective diabetes management. This study evaluated and compared the knowledge of metformin-related vitamin B-12 deficiency and its neurological implications among medical and pharmacy graduates in Libya. A cross-sectional survey was conducted from February to May 2024 among 100 recent graduates (50 medical and 50 pharmacy). The self-designed questionnaire assessed 27 questions that structured knowledge of diabetes pathophysiology, metformin pharmacotherapy, mechanisms of vitamin B-12 deficiency, and its potential association with Alzheimer's disease. Comparisons were performed using the Chi-square test. Pharmacy graduates demonstrated higher overall knowledge of diabetes management compared with medical graduates (77.2% vs. 66.4%; OR=1.72; $p<0.001$) and significantly greater awareness of metformin-related complications, particularly vitamin B-12 deficiency. Knowledge regarding metformin-vitamin B-12 interactions and Alzheimer's disease was comparable between groups. Although most participants recognized dietary sources and monitoring recommendations, inconsistencies were observed in clinical application. Pharmacy graduates demonstrated superior awareness of metformin safety; nevertheless, enduring deficiencies in knowledge across medical and pharmacy graduates indicate a critical need for integrated interprofessional education to advance preventive care and risk mitigation in type 2 diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by persistent hyperglycemia due to impaired insulin secretion and/or defective insulin action. DM has emerged as one of the most significant public health challenges globally, affecting hundreds of millions of people and with numbers rising rapidly [1, 2]. Over 370 million people have DM, and that number is expected to increase to 552 million by 2030, making it one of the leading causes of death and disability worldwide. DM substantially contributes to morbidity and mortality, accounting for significant proportions of new cases of legal blindness, end-stage renal disease, and non-traumatic lower limb amputations, while doubling to quadrupling the risk of cardiovascular disease and stroke [3-7]. In North Africa, the burden is particularly concerning, with prevalence

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ISSN: 2958-3101 print

estimates reaching 10.5% among adults aged 20-79 years and showing an upward trend [8]. Type II diabetes mellitus (T2DM) represents over 90.0%-95.0% of all DM cases worldwide [9]. It arises primarily from insulin resistance combined with progressive beta-cell dysfunction, driven by genetic susceptibility and modifiable risk factors, including obesity, a sedentary lifestyle, and a poor diet [8, 10]. T2DM manifests with a cluster of cardiometabolic abnormalities such as obesity, hypertension, dyslipidemia, nephropathy, and chronic inflammation [11]. The complex pathophysiology involves multiple defects: pancreatic alpha- and beta-cell dysfunction, reduced incretin effect, increased hepatic gluconeogenesis, impaired peripheral glucose uptake, enhanced renal glucose reabsorption, and altered gastrointestinal glucose absorption [12]. Management of T2DM combines lifestyle modification with medication options, including sulfonylureas, glitazones, glinides, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors, each with distinct mechanisms and safety profiles [9, 13, 14]. Metformin remains the first-line therapy in most international guidelines because of its effectiveness, weight neutrality, low risk of hypoglycemia, and additional benefits including reduced hepatic gluconeogenesis and improved insulin sensitivity [5, 16].

Vitamin B-12 is primarily obtained from animal-sourced foods such as red meat, shellfish, eggs, milk, and other dairy products. Vitamin B-12 plays a critical role in DNA synthesis, red blood cell formation, and neurological function. it is normal serum concentrations range from 160 to 950 pg/mL [17]. Epidemiological evidence links elevated homocysteine and low B-12 status with about 50.0% increased dementia risk, including Alzheimer's disease (AD) [18]. Metformin-induced B-12 deficiency thus represents a modifiable pathway potentially linking DM treatment to neurocognitive decline [19]. Healthcare professionals play critical roles in mitigating these risks [20]. Pharmacists provide medication counseling, B-12 screening facilitation, adherence support, and interdisciplinary collaboration [3, 21, 22]. Physicians handle diagnosis via HbA1c, fasting glucose, and OGTT; prescribe and titrate therapy; monitor glycemic control; and order periodic B-12 assessment in long-term metformin users [23]. Both health professionals must recognize the metformin-B12-AD pathway to enable early intervention through supplementation and monitoring [24]. This study aims to compare knowledge levels among graduated pharmacy and medical students regarding metformin-induced vitamin B-12 deficiency and its potential association with AD.

Materials and methods

A cross-sectional study was conducted in February to May 2024 included 100 pharmacy and medical graduate in Zawia City, Libya. This study aimed to compare the knowledge levels regarding metformin-induced vitamin B-12 deficiency and its potential association with AD and to identify the differences in knowledge between the two professional groups (pharmacy and medical recent graduates). Data were collected using a structured, self-administered offline questionnaire distributed to graduates working in community pharmacies and hospital settings. The questionnaire consists of 27 items organized into seven sections, including multiple-choice and dichotomous yes/no questions. The questionnaire covering demographic and professional characteristics, knowledge of DM, antidiabetic medications with a focus on metformin, vitamin B-12 and its physiological role, the interaction between metformin and vitamin B-12, neurological complications including AD, and graduates' professional role in patient education and sources of information.

Ethical consideration and consent process: The approval was obtained from the scientific committee of the Faculty of Pharmacy, University of Zawia (2024) before starting the study. Written consent from the participants was obtained and was completely voluntary. All the needed information was kept confidential.

Statistical analysis: Descriptive statistics were used to summarize the data and are presented as frequencies and percentages. The Chi-square test was applied to compare knowledge levels between pharmacy and medical graduates, with statistical significance set at $p<0.05$.

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Results

Demographic characteristics of participants: The study included 100 participants, with an equal distribution between medicine and pharmacy graduates (50.0% each). The majority of the participants were female subjects (75.0%) and aged between 25 years and 30 years (44.0%). Most of the participants were from Zawia City (62.0%), followed by Tripoli City (27.0%). However, more than half of the participants reported having more than three years of work experience (**Table 1**).

Table 1: Demographics of the Libyan health professional participants

Variable	Frequency (%)
Gender	
Male	25 (25.0)
Female	75 (75.0)
Age (year)	
20-25	17 (17.0)
25-30	44 (44.0)
30-35	39 (39.0)
City of origin	
Tripoli	27 (27.0)
Zawia	62 (62.0)
Sabratha	04 (04.0)
Surman	02 (02.0)
Zuwarah	05 (05.0)
Academic degree	
Bachelor Pharmacy	50 (50.0)
Bachelor Medicine	50 (50.0)
Work experience	
6-12 months	30 (30.0)
1-2 years	08 (08.0)
2-3 years	10 (10.0)
> 3 years	52 (52.0)

Knowledge about DM: Pharmacy participants had a higher proportion of correct answers for T2DM mechanisms, diagnostic cut-off, and the most common complication, with a significant difference ($p<0.05$). Knowledge of the general DM definition and diabetic criteria showed no significant difference. Participants' knowledge about DM was assessed through multiple questions. The results are summarized in **Table 2**.

Table 2: Knowledge about diabetes mellitus

Question	Correct answer Medicine (n=50)	Correct answer Pharmacy (n=50)	P value
What is diabetes mellitus?	44 (88.0%)	39 (78.0%)	0.287
Type 2 diabetes mellitus occurs when	19 (38.0%)	30 (60.0%)	0.045*
When is a person considered diabetic?	47 (94.0%)	46 (92.0%)	0.999
Cut-off point for diagnosing diabetes	35 (70.0%)	43 (86.0%)	0.05*
The most common complication of type 2 diabetes	21 (42.0%)	35 (70.0%)	0.001*

*Significant at $p < 0.05$

Antidiabetic medications and metformin: Pharmacy participants were significantly more aware of metformin's most common complication. Other aspects of metformin knowledge showed no significant differences. Participants' knowledge regarding antidiabetic medications, specifically metformin, was evaluated (**Table 3**).

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Table 3: Knowledge about antidiabetic medications and metformin

Question	Correct answer Medicine (n=50)	Correct answer Pharmacy (n=50)	P value
The most common antidiabetic medication	32 (64.0%)	29 (58.0%)	0.682
The most common complication of metformin	21 (42.0%)	40 (80.0%)	0.001*
Mechanism of metformin action	34 (68.0%)	29 (58.0%)	0.408

* Significant at p<0.05

Vitamin B-12 knowledge: **Table 4** shows that pharmacy participants were statistically significantly more familiar with vitamin B-12 than medicine participants. Knowledge regarding its role and the most common complications of vitamin B-12 deficiency showed no significant difference between the pharmacy and medicine groups.

Table 4: Vitamin B-12 knowledge

Question	Correct answer Medicine (n=50)	Correct answer Pharmacy (n=50)	P value
Familiar with vitamin B-12	41 (82.0%)	48 (96.0%)	0.05*
The most essential role of vitamin B-12	40 (80.0%)	41 (82.0%)	0.999
The most common complication of B-12 deficiency	42 (84.0%)	39 (78.0%)	0.611

*Significant at p<0.05

Metformin and vitamin B12 interaction: In **Table 5**, participants of both groups were asked about metformin-induced B-12 deficiency and related clinical monitoring. Knowledge about the interaction between metformin and vitamin B-12, its clinical implications, and dietary influence showed no significant differences between the two participants.

Table 5: Knowledge of metformin-B-12 interaction

Question	Correct answer: Medicine (n=50)	Correct answer: Pharmacy (n=50)	P value
Aware of metformin -B-12 interactions	38 (76.0%)	36 (72.0%)	0.820
How does metformin affect B-12 levels	43 (86.0%)	45 (90.0%)	0.760
Onset of neurological symptoms	21 (42.0%)	15 (30.0%)	0.298
Monitor serum B-12 in metformin patients	36 (72.0%)	33 (66.0%)	0.666
Dietary role in B12 levels	43 (86.0%)	44 (88.0%)	0.999

No significant difference between the groups

Neurological complications and AD: Knowledge regarding neurological complications associated with metformin-induced B12 deficiency, including AD, was evaluated and presented in **Table 6**. Thus, knowledge about progressive neurological complications, main risk factors for B-12 deficiency induced AD, and the mechanism linking B-12 deficiency leading to AD was similar between the medicine and pharmacy participants, with no statistically significant differences.

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Table 6: Neurological complications and Alzheimer's disease

Question	Correct answer Medicine (n=50)	Correct answer Pharmacy (n=50)	P value
Progressive neurological disease	41 (82.0%)	40 (80.0%)	0.999
Main risk factor for B1deficiency-induced Alzheimer disease	38 (76.0%)	40 (80.0%)	0.810
Mechanism leading to Alzheimer disease	30 (60.0%)	27 (54.0%)	0.686

Professional role and sources of information: Participants reported their role in educating diabetic patients, and their source of knowledge is presented in **Table 7**. Most of the participants reported that giving advice and guidance was their main professional role, and that previous academic studies were their primary source of knowledge. No significant differences were observed between the medicine and pharmacy participants.

Table 7: Professional role and sources of information

Question	Answer	Medicine (n=50)	Pharmacy (n=50)	P value
Role in educating patients	Giving advice and guidance	23 (46.0%)	25 (50.0%)	0.592
	Changing medication	4 (8.0%)	1 (2.0%)	
	Advising consultation	20 (40.0%)	21 (42.0%)	
	I do notknow	3 (6.0%)	3 (6.0%)	
Source of information	Personal communication	6 (12.0%)	6 (12.0%)	0.137
	Books	11 (22.0%)	3 (6.0%)	
	Social media	4 (8.0%)	6 (12.0%)	
	Previous studies	29 (58.0%)	35 (70.0%)	

Overall knowledge comparison between medicine and pharmacy participants: The total correct answers in each knowledge domain were calculated to compare overall knowledge (**Table 8**). Pharmacy participants demonstrated a significantly higher level of knowledge about DM compared with the medical participants, as reflected by a greater proportion of correct responses (77.2% versus 66.4%). This difference was significant, with an odds ratio of 1.72 and a 95.0% confidence interval of 1.18-2.51 ($p<0.001$). In contrast, there were no significant differences between medicine and pharmacy participants in overall knowledge across the domains of metformin, vitamin B12, and AD (**Figure 1**).

Table 8: Overall, knowledge comparison between medicine and pharmacy participants

Knowledge Domain	Medicine: sum (%)	Pharmacy: sum (%)	Odds ratio (95% CI)	P value
Diabetes mellitus	166 (66.4%)	193 (77.2%)	1.72 (1.18-2.51)	0.001*
Metformin	87 (58.0%)	98 (65.3%)	1.36 (0.86-2.15)	0.19
Vitamin B12	123 (82.0%)	128 (85.3%)	1.27 (0.66-2.46)	0.43
Metformin with vitamin B12 interaction	181 (72.4%)	173 (69.2%)	0.86 (0.59-1.26)	0.43
Alzheimer's disease	109 (72.7%)	107 (71.3%)	0.93 (0.57-1.52)	0.79

*Significant at $p<0.05$

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ISSN: 2958-3101 print

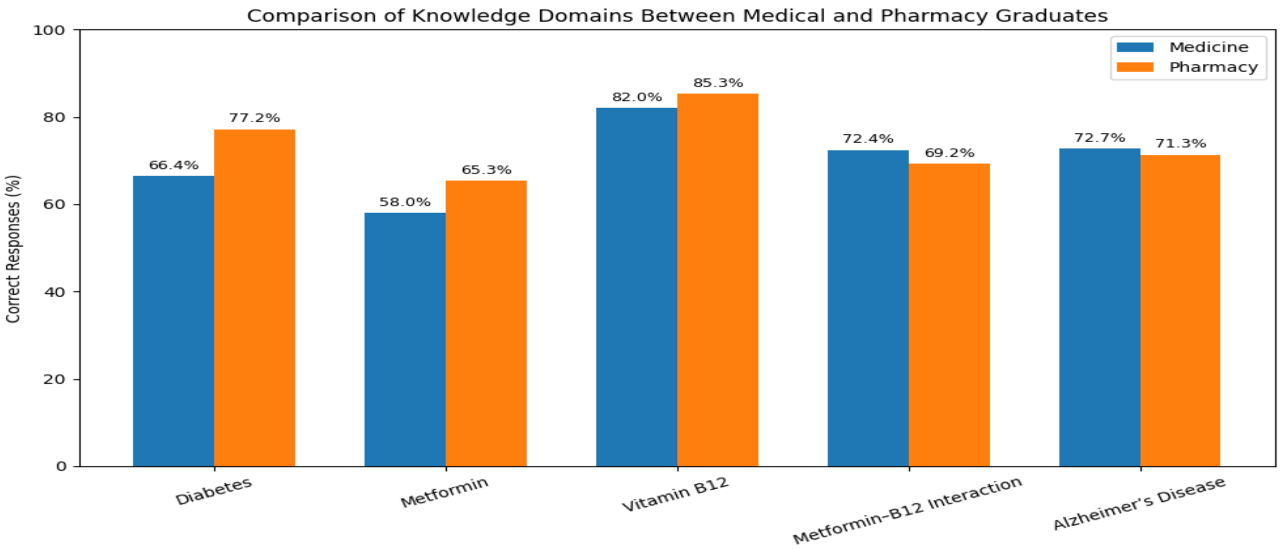

Figure 1: Overall, knowledge comparison between medicine and pharmacy participants

Discussion

Recently, there has been growing concern about the potential link between metformin-induced vitamin B-12 deficiency and AD. This study compares the knowledge of this association among recent Libyan medical and pharmacy graduates. The majority of participants were female and aged 25-30 years. Most of the participants were from Zawia, followed by Tripoli. More than half of the participants reported having more than three years of work experience. A key finding of this study was the significantly higher level of knowledge among pharmacy participants regarding the pathophysiology of T2DM, diagnostic cut-off value, and the most common complications associated with T2DM. These results align with the previous findings, which report that pharmacy graduates often possess a strong knowledge of chronic disease mechanisms and management strategies due to their curriculum's focus on pharmacotherapy and disease monitoring [**25**]. The observed difference may reflect a greater exposure of pharmacy students to diabetes-specific education, patient counseling, and guideline-based management approaches [26]. In contrast, participants in the medicine and pharmacy did not significantly differ in their understanding of the core diagnostic criteria and the general description of DM. This may suggest that fundamental DM concepts are adequately covered in medical and pharmacy education, which is consistent with the findings reported among healthcare students in other regions [27]. In this study, Most of the pharmacy and of the medical graduates correctly identified that a patient must have an HbA1c level greater than 6.5% and a fasting blood glucose level greater than 126 mg/dL to be classified as diabetic. This brings into line with the diagnostic criteria established by the American Diabetes Association, ADA [28]. Participants from medicine and pharmacy showed comparable knowledge about the most common antidiabetic medications and metformin mechanism of action. However, pharmacy participants were notably more knowledgeable about the most common complication of metformin, especially vitamin B12 deficiency. This result agrees with the previous study, which indicates that pharmacy graduates possess a stronger understanding of drug safety, adverse reactions, and medication counseling [29, 30]. This trend may stem from pharmacy trainees' direct patient interactions and the clinical pharmacy curriculum's emphasis on adverse drug reactions and disease-related pharmacotherapy [31, 32]. Metformin is the most widely prescribed oral diabetic pharmacological mono- or combination therapy. It is suggested for most T2DM patients due to its efficacy, minimal risk of hypoglycemia, body weight neutrality, cardioprotective impact, and affordability. Metformin acts by reducing hepatic gluconeogenesis and improving peripheral insulin sensitivity through activation of AMP-activated protein kinase [33]. The moderate and comparable correct response rates between both groups suggest a knowledge gap in guideline-based DM management, despite DM being included in medical and pharmacology curricula, a finding consistent with a previous study [34].

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ISSN: 2958-3101 print

Vitamin B-12 is an essential micronutrient needed for optimal hematopoietic and neurological function, so deficiency leads to serious consequences represented in peripheral neuropathy and irreversible nerve tissue damage [35, 36]. Pharmacy participants were significantly more familiar with vitamin B-12, although both groups demonstrated similar knowledge regarding its physiological role and deficiency-related complications. This may reflect a broader exposure of pharmacy students to nutritional biochemistry and drug-nutrient interactions [37]. Vitamin B-12 deficiency can lead to hematological and neurological complications in patients receiving long-term metformin therapy [38]. The comparable knowledge observed between medicine and pharmacy participants regarding B-12 complications suggests adequate baseline awareness; however, a previous study has shown that this knowledge does not always translate into routine clinical screening or monitoring [39]. Despite growing evidence linking long-term metformin use to reduced vitamin B-12 levels, the ADA recommends periodic assessment of vitamin B12 levels in patients receiving long-term metformin. No significant difference was observed between the two groups regarding knowledge of metformin-induced B-12 deficiency, its neurological manifestations, or monitoring practices. This finding aligns with prior studies indicating that, despite existing awareness of this interaction among healthcare professionals, the consistent application of recommended screening and monitoring protocols in clinical practice remains inconsistent [40]. The reported prevalence of vitamin B-12 deficiency among metformin users ranges from 6.0% to 30.0%, influenced by ethnicity, baseline vitamin B-12 level, metformin dose, and duration of therapy. Long-term metformin therapy has been associated with a progressive decline in vitamin B-12 levels and an increased risk of deficiency [38]. In the present study, 42.0% and 30.0% of graduates from the two schools reported encountering neurological manifestations of metformin-associated vitamin B-12 deficiency, typically emerging after two or more years of treatment. Consistently, large prospective study documented a 20.3% prevalence after exceeding nine years of metformin use [41]. The daily dose and the duration of metformin treatment have been identified as significant predictors of vitamin B-12 deficiency. Evidence suggests that metformin dose and treatment duration are significant predictors of deficiency, with thresholds of more than four years and ≥ 1100 mg/day identified in prior research [42]. Variability in findings may be attributed to differences in diagnostic criteria, dosing regimens, and pre-existing subclinical vitamin B-12 deficiency, which could accelerate symptom onset. Conversely, respondents who did not report such cases may have formed differing perceptions due to limited clinical exposure and diagnosis [43]. The same group of graduates was asked whether they routinely monitor serum vitamin B-12 level in patients with DM treated with metformin. Among medical graduates, 72.0% reported that they performed such monitoring. Similarly, 66.0% of pharmacists working in clinical settings and community pharmacies indicated that they routinely assess vitamin B-12 levels.

It is commonly known that for DM patients, using metformin, obtaining vitamins and trace minerals organically is the best option. Most respondents demonstrated a high level of agreement regarding the influence of dietary habits on vitamin B-12 status. Specifically, correctly identified the consumption of animal-derived foods as the primary dietary source of vitamin B-12. This understanding is consistent with evidence from the Harvard School of Public Health, which emphasizes that vitamin B-12 is obtained naturally through the intake of meat and dairy products [44]. The medicine and pharmacy participants showed similar knowledge regarding neurological complications and the potential association between vitamin B-12 deficiency and AD. Literature suggests that vitamin B-12 deficiency may contribute to learning and cognitive impairments through mechanisms involving homocysteine elevation and neuronal damage [45, 46]. However, the relationship between metformin use, B-12 deficiency, and AD remain complex and not clearly understood [23]. The comparable knowledge observed may reflect the multifactorial nature of neurodegenerative diseases and the limited emphasis placed on drug-nutrient interactions in the context of cognitive disorders during undergraduate training. Most of the respondents showed similar understanding, with 82.0% of medical graduates and 80.0% of pharmacy graduates identifying AD as the main cognitive disorder associated with

ISSN: 2789-1895 online
ISSN: 2958-3101 print

vitamin B-12 deficiency. These findings are consistent with evidence from a case-control study showing a significantly higher risk of AD among individuals with reduced plasma vitamin B-12 [45]. One proposed mechanism underlying this association involves elevated homocysteine levels resulting from vitamin B-12 deficiency. Impaired homocysteine metabolism has been independently linked to cognitive decline and AD. In the current study, both graduates showed comparable understanding of this mechanism, with the majority identifying homocysteine as the key risk factor. This perception is supported by large cohort studies and meta-analyses demonstrating a strong association between elevated homocysteine levels and increased AD risk [46]. Medicine and pharmacy participants reported that their primary professional role in DM care involved providing advice and guidance, and that previous academic study was their main source of knowledge [14, 47]. This finding underscores the pivotal role of undergraduate education in shaping professional competence and underscores the need for curricula that integrate clinical guidelines with practical decision-making skills [26, 31]. When overall knowledge scores were compared, pharmacy participants demonstrated significantly higher knowledge regarding DM, while no differences were found for metformin, vitamin B-12, metformin-B-12 interaction, or AD. These findings suggest that the observed differences are domain-specific rather than global, reinforcing the complementary roles of medicine and pharmacy graduates in DM management and patient care. Thus, both healthcare professionals can provide comprehensive care to patients, considering both the clinical aspects of AD and the medication management of metformin.

Conclusion: This study suggests that while medicine and pharmacy graduates demonstrated a reasonable level of knowledge across most domains, pharmacy graduates showed superior knowledge in specific diabetes-related areas, whereas knowledge in medication-related and neurological domains was largely comparable between the two groups. The knowledge gap between the graduates can be filled with the aid of inter-professional cooperation and continued education.

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Acknowledgements: The authors would like to thank all the pharmacists and physicians for their contributed to this study.
Authors' contribution: ERI conceived, designed the study and collected data. FYA contributed to data analysis. WMA performed analysis. FYA drafted and reviewed the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for its contents.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: The authors completely observed ethical issues, including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.
Generative AI disclosure: No Generative AI was used in the preparation of this manuscript.