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Knowledge and Perception of Triple Whammy Among Pharmacists in the Kingdom of Saudi Arabia

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Abbreviations: GFR: Glomerular Filtration Rate; ACEIs: Angiotensin-Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ADR: Adverse Drug Reactions; RAAS: Renin–Angiotensin–Aldosterone System; CKD: Chronic Kidney Disease; AKI: Acute Kidney Injury

ABSTRACT

Introduction: Renin-angiotensin system inhibitors (ACEI/ARB-II), diuretics, and NSAIDs, a combination known as "Triple Whammy", can result in decreased glomerular filtration rate (GFR) and acute kidney injury (AKI).

Objectives: To measure the Knowledge and awareness of Saudi pharmacists about the risk of triple whammy.

Methods: Cross-sectional survey study was conducted from September 2020 to October 2020 in the Kingdom of Saudi Arabia, in different regions and it included hospitals and community Saudi pharmacists.

Results: Males more common to participate in this study, the percentage was 65% and females about 35%. Non-Saudi pharmacists are participating in this study about 4.3% but the Saudi participating about 95.7 %. Most of the pharmacists are working in the field of pharmacy in KSA had a bachelor's degree in the pharmacy 65.3 % master's degree 15.3 % and PhD. only 1.7%, most our participating not know about Triple Whammy in about 62.7% and who know about this is 37%.

Conclusion: Treatment with ACEI, ARB-II, diuretics, and/or NSAIDs shows a high incidence of hospitalization episodes due to AKI (Rosa Maria Garcia Camin et al ,2015, Spain), the percentage of pharmacists do not know anything about Triple Whammy in KSA is large 62.7% there is highly needed to make continuous medical education to increase the knowledge of pharmacists about the problem of the combination of these drugs.

Introduction and Literature Review

NSAIDs are associated with an increased risk of AKI, due to blockade of the COX-2 enzyme preventing prostacyclin synthesis, which causes afferent arteriolar vasoconstriction [1]. Inhibition is maximal when steady state plasma concentrations are reached, usually after three to seven days of treatment. The risk of AKI is highest in the first month of NSAID ACE inhibitors or ARBs generally preserve renal function. However, these medicines can also treatment. Pre-renal acute kidney injury (AKI) results from glomerular hemodynamic alterations leading to reduced glomerular filtration rate (GFR) with no parenchymal compromise. Renin-

angiotensin system inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics, are highly prescribed drugs that are frequently administered together. Double and triple associations have been correlated with increased pre-renal AKI incidence, termed "double whammy" and "triple whammy", respectively (Prieto-García L, et al. [1]).

In the early 2000s, pharmacovigilance reports coined the "triple whammy" expression to illustrate the risk of renal injury associated with combinations of three of the following drugs, NSAIDs, ACEIs or ARBs and diuretics. More recently, Lapi, et al. [2]. confirmed this risk of "triple whammy" in the general population, using the UK Clinical Research Practice Datalink. In their cohort of 487,372 antihypertensive-treated patients, followed-up during 5.9 ± 3.4 years, triple therapy was associated with a 31% increased AKI, compared to patients treated with diuretic and ACEI or ARB only Increased AKI risk was maximal in the first 30 days of the associations. In addition, the use of long half-lives NSAIDs (more than 12 hours) tended to be associated with a higher increased risk of AKI, although there was no significant interaction between NSAIDs half-lives and the triple association. In 2012, published an observational study investigating drug interactions between NSAIDs and antihypertensive drugs in the French Pharmacovigilance Database found that around 25% of associations between NSAIDs and antihypertensive were associated with a "serious" Adverse Drug Reactions (ADR). Most of them were AKIs (92.8%). Thus, performed a secondary analysis of this study, using a case/non-case approach, aiming to investigate whether the number of drugs associated between NSAIDs, ACEIs, ARBs and diuretics was associated to disproportionate reporting of AKI [3]. Concurrent use of NSAIDs, renin–angiotensin–aldosterone system (RAAS) blockers, and diuretics is strongly related to the occurrence of AKI; this combination of drugs is called the "triple-whammy". AKI induced by the triple-whammy is caused by a combination of pharmacological activities:

(1) NSAIDs lead to renal afferent arteriolar constriction;

(2) RAAS blockers cause hemodynamic reduction in the glomerular-filtration rate due to efferent arteriolar dilation, and

(3) diuretics lead to hypovolemia [1,3].

Thus, Japanese guidelines recommend that particular attention be paid to prescription of triple-whammy to patients with chronic kidney disease (CKD) because these combinations are likely to induce disease progression. In clinical-pharmacy-practice experience, triple-whammy prescriptions often occur when the three drug types are prescribed by different clinical departments. For example, NSAIDs may be prescribed by an orthopaedic surgery department, whereas RAAS blockers and diuretics may be prescribed by an internal medicine department. However, no reports have assessed the extent to which this occurs [4].

Literature Review

Taking two or more of the identified drugs was associated with significant renal impairment but did not correlate with heart failure or other diseases for which the drugs might have been prescribed. Care is necessary to balance the demonstrated advantages of these medications against the risk of inducing renal failure (Katarzyna K, et al. [5]). Triple whammy induces an overt AKI and NSAID including double whammies cause a subclinical AK Shows AKI associated with NSAID users of any combination of RASI and/or diuretics. The intervention improved the prescription and reduced the number of patients on TW combination. Treatment with ACEI, ARB-II, diuretics and/or NSAIDs shows a high incidence of hospitalization episodes due to AKI (Rosa Maria Garcia Camin, et al. [6]). The results indicate a degree of acute kidney injury prior (AKI) at-risk prescribing. There are opportunities to empower people to self-manage at-risk medicines during periods of acute illness (Dianne Vicary, et al. [7]).

Diuretics in monotherapy, dual and triple combination therapy (Triple Whammy) have an elevated incidence of AKI. Dual therapies including diuretics show the same incidence of AKI as the Triple Whammy. The profile of the at-risk patient is an elderly patient with an underlying renal or cardiac disease. The problem does not seem to be the drug itself but the onset of a concurrent disease-causing hypovolemia. Monitoring renal function and potassium levels is recommended when these therapies are initiated and in situations of concurrent disease (Garcia Camin, et al. [8]). Taking two or more of the identified drugs was associated with significant renal impairment but did not correlate with heart failure or other diseases for which the drugs might have been prescribed. Care is necessary to balance the demonstrated advantages of these medications against the risk of inducing renal failure.

Rational

ARBs or ACEIs, NSAIDs and diuretics, are highly prescribed together, therefore prescribers should remember that using these medicines can increase the risk of AKI.

Aims

- To measure knowledge and awareness of pharmacists in Saudi Arabia about the risk of triple whammy.
- To regular medicine reviews to avoid inadvertent concurrent prescribing of an ACEIs /ARBs, diuretics and NSAIDs.
- To drug interaction checkers built into patient management system.
- To avoid oral NSAIDs when managing long-term pain

conditions in patients taking ACEIs or ARBs and diuretics, mainly hypertension patients.

- Patients taking an ACEI or ARB and a diuretic should be warned of the risks of using NSAIDs and should be advised to avoid purchasing OTC NSAIDs.

Methodology

Design and Setting

cross-sectional survey study conducted from September 2020 to October 2020 in the Kingdom of Saudi Arabia, in different regions and it include hospital and community pharmacists and pharmacy technicians.

Data Collection

The data collected via online survey which be sent to targeted population via email or other online approaches.

Sample Size and Statistical Analysis

The sample size is estimated to be 300 Pharmacist and pharmacy technician in Saudi Arabia.

Results

According to the age of our participating it was fount high percentage of them between 30- 39 years old 61.7% but the age between 50 – 60 years old about 1% this reflecting that the middle age group between 30 – 39 years old are the most pharmacists working in KSA. (Tables 1 & 2). According to the gender, it was found that males more common to participate in this study near double fold, the percentage was 65% comparing to females about 35%. Non-Saudi pharmacists are participating in this study are too small comparing to Saudi pharmacists about 4.3% but the Saudi participating about 95.7 %. (Tables 3 & 4 and Figures 1-5). Most of the pharmacists are working in the field of pharmacy in KSA with had bachelor's degree in the pharmacy 65.3 % master's degrees 15.3 % and Ph.D. only 1.7% of this is reflecting there are needs to encourage the young pharmacists to get a higher education degree. Near half of our participating had pharmacists in the current position about 49.7 % and the clinical pharmacists still low in percentage about 12 %. Most of our participating are working in the field of the pharmacy from 1 year to 10 years about 59.7. (Figures 6-9). Many of our participating are working in Public Hospital Pharmacy about 70.7 % and Primary Healthcare Centre about 16.7 % the private hospital only 3.3 % (Tables 5-6). this is reflecting that most of Saudi pharmacists like to work MOH hospitals rather than private hospitals. Most of our participating from Najran and Jeddah and Riyadh and there is many participating all over KSA areas.

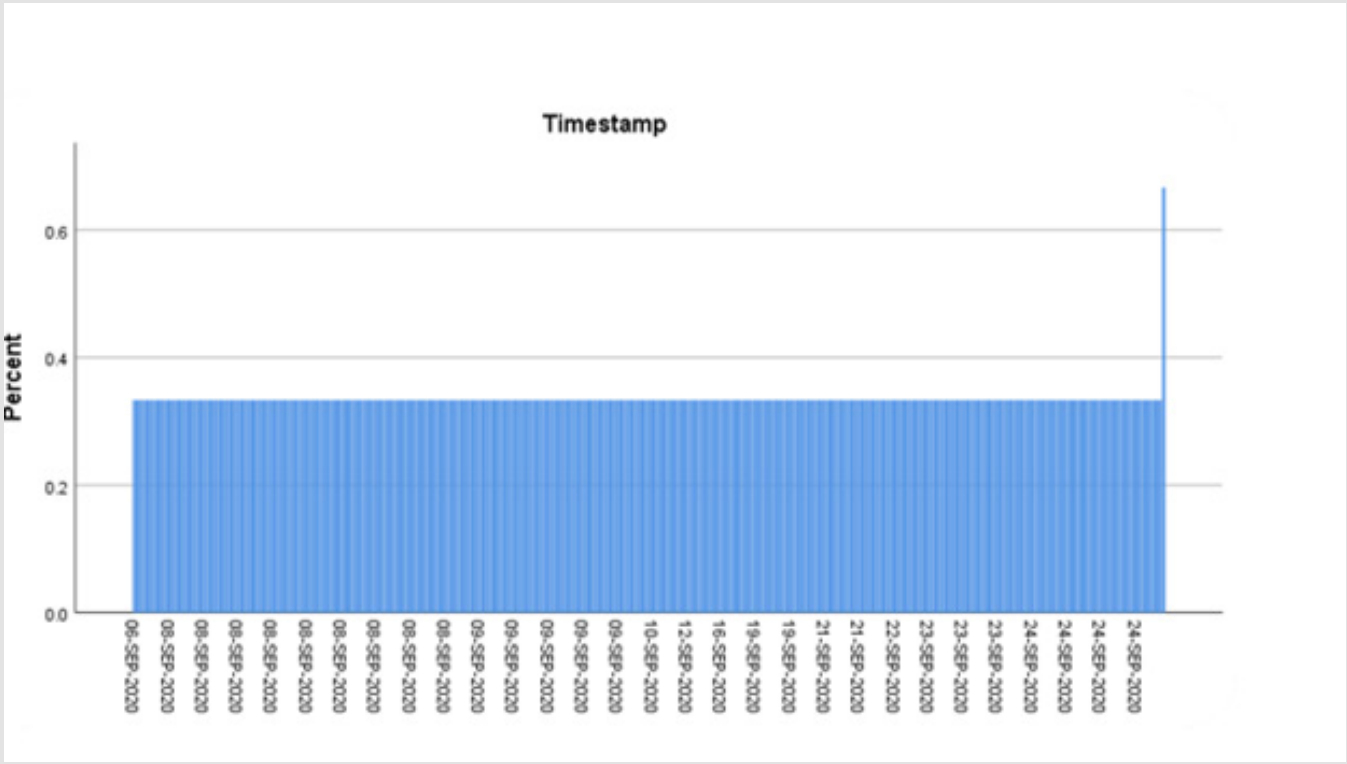

Figure 1: Bar chart showing timestamp.

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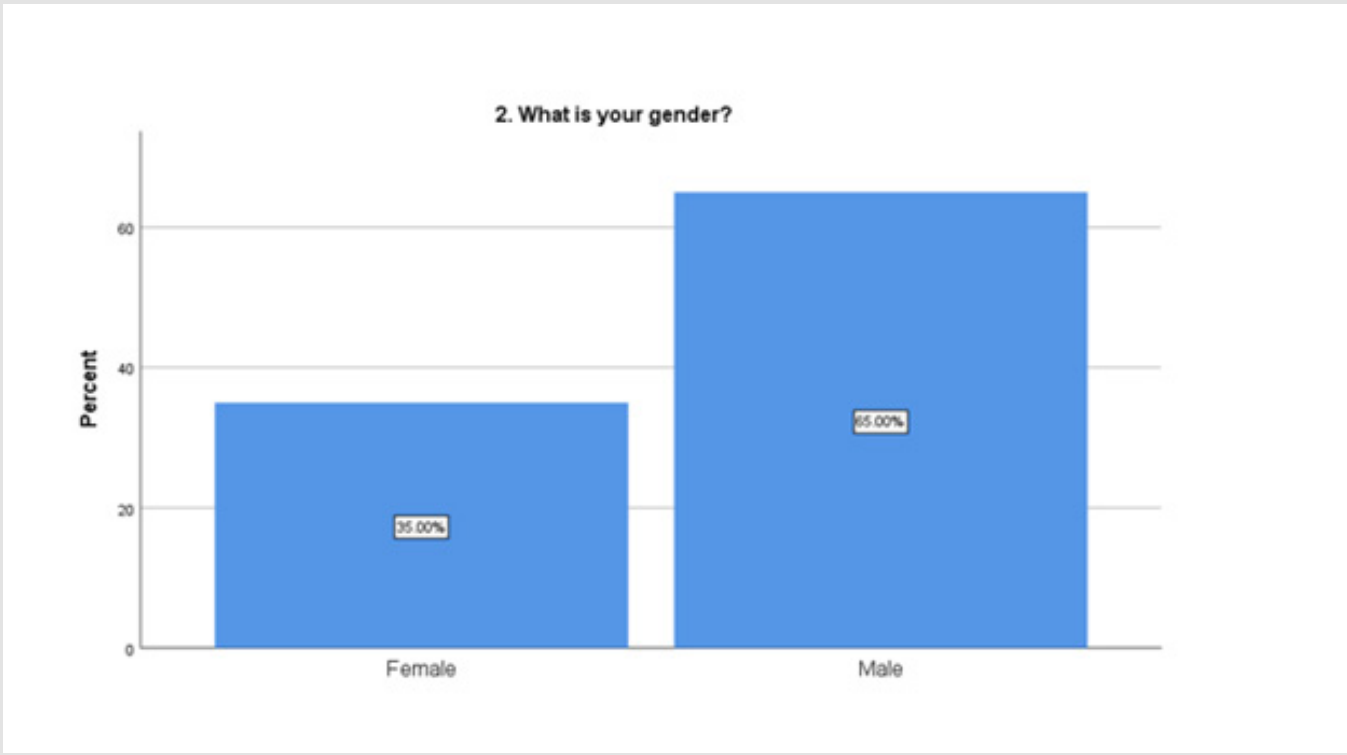

Figure 2: Bar chart showing gender.

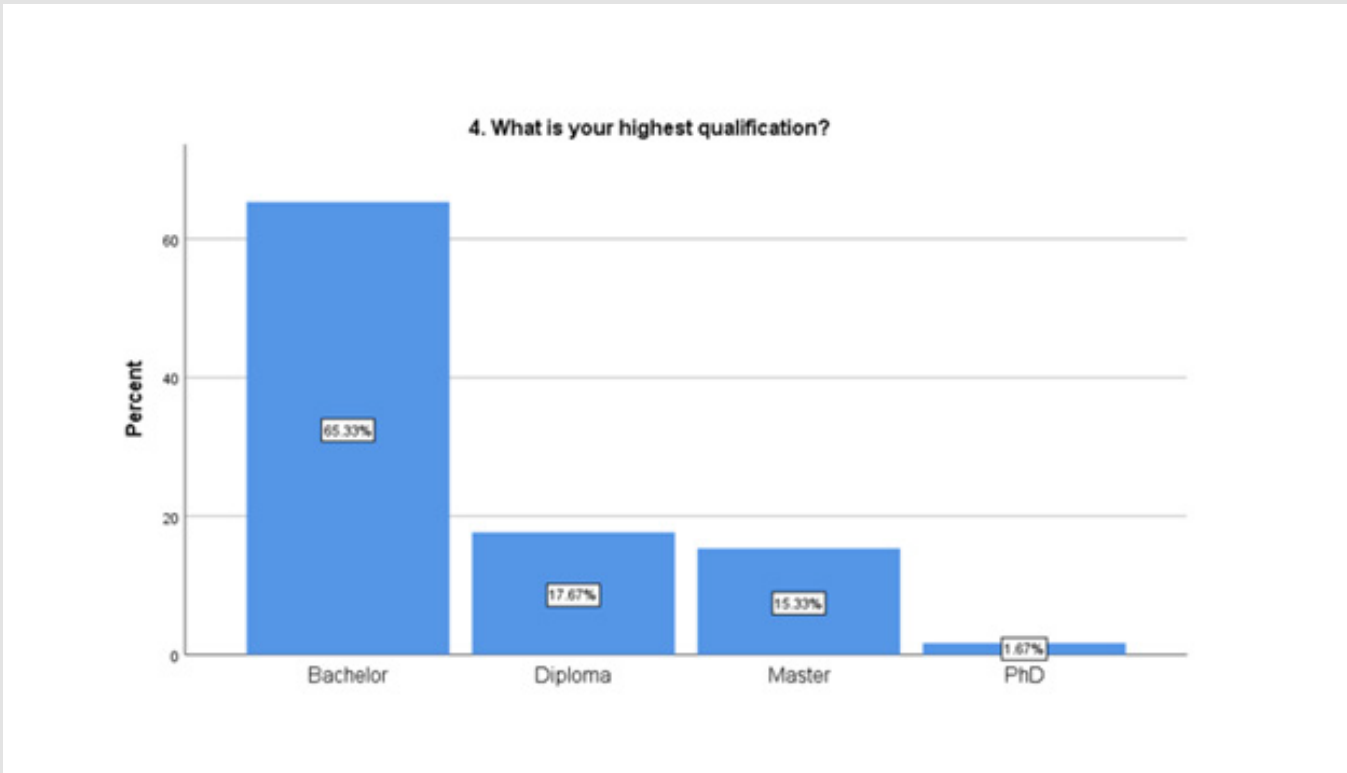

Figure 3: Bar chart showing qualification.

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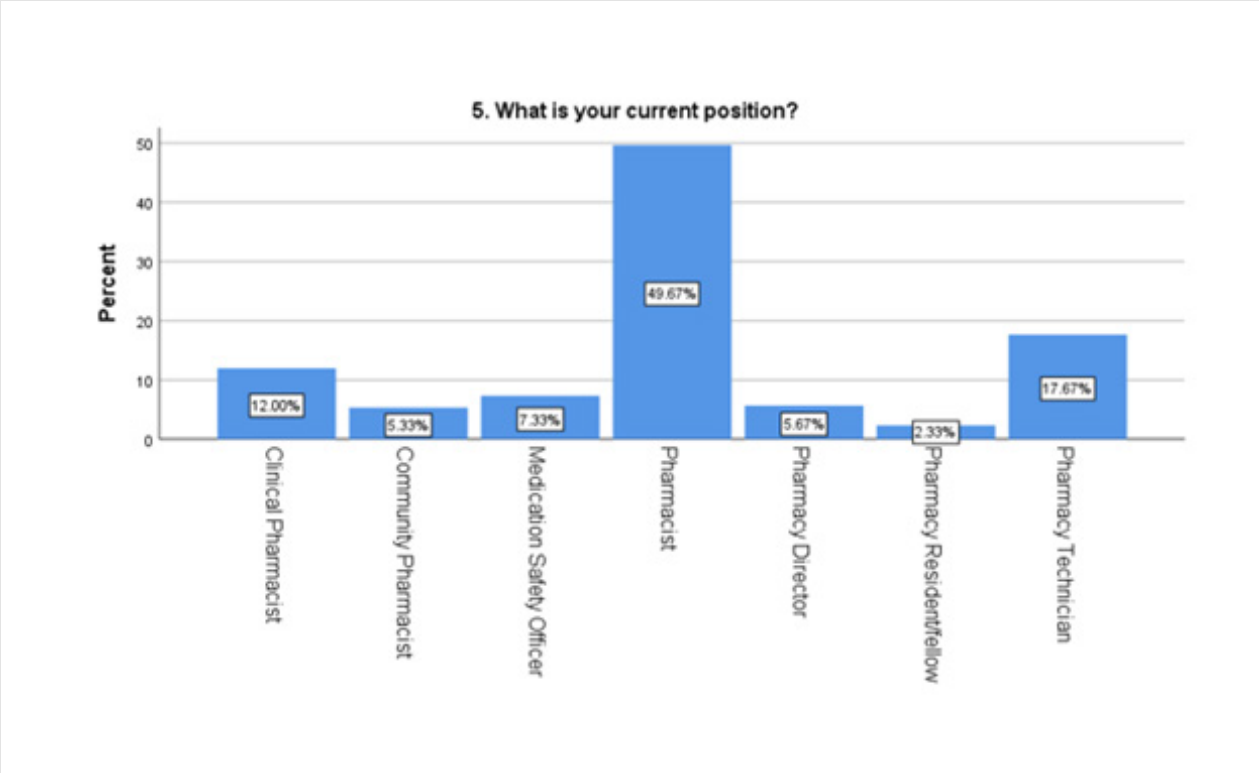

Figure 4: Bar chart showing qualification.

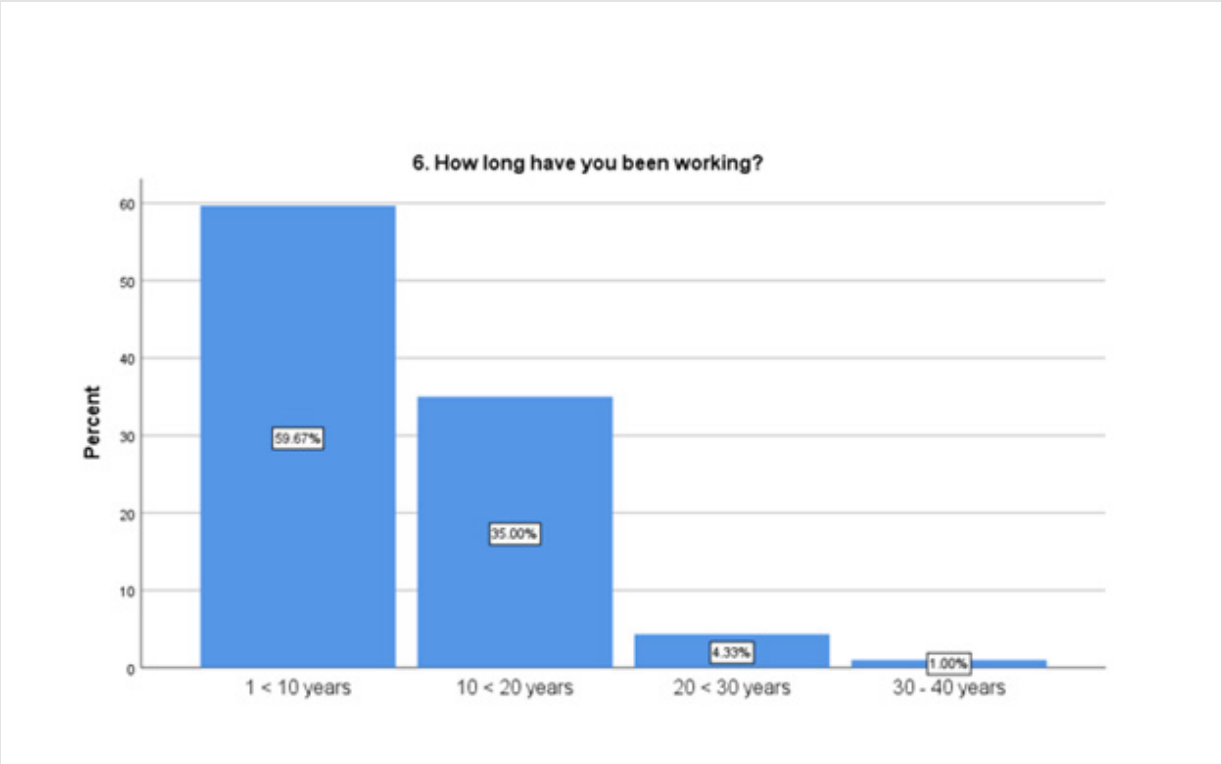

Figure 5: Bar chart showing experience.

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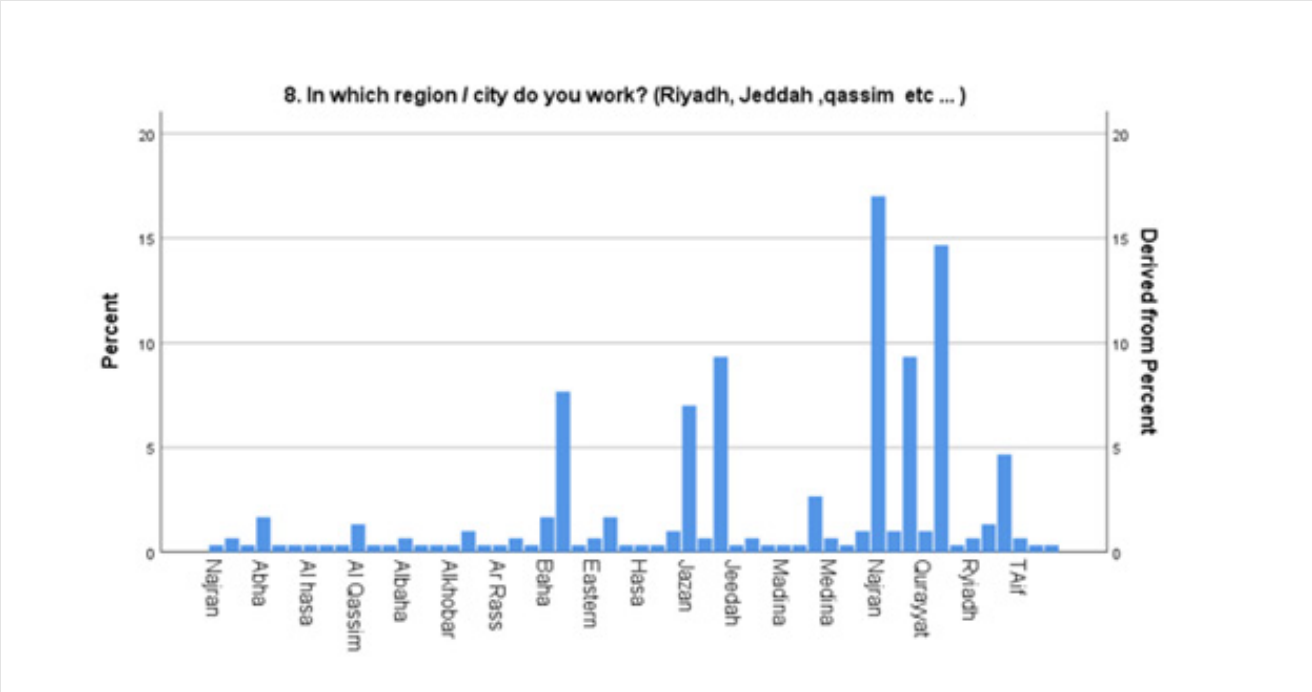

Figure 6: Bar chart showing place of work.

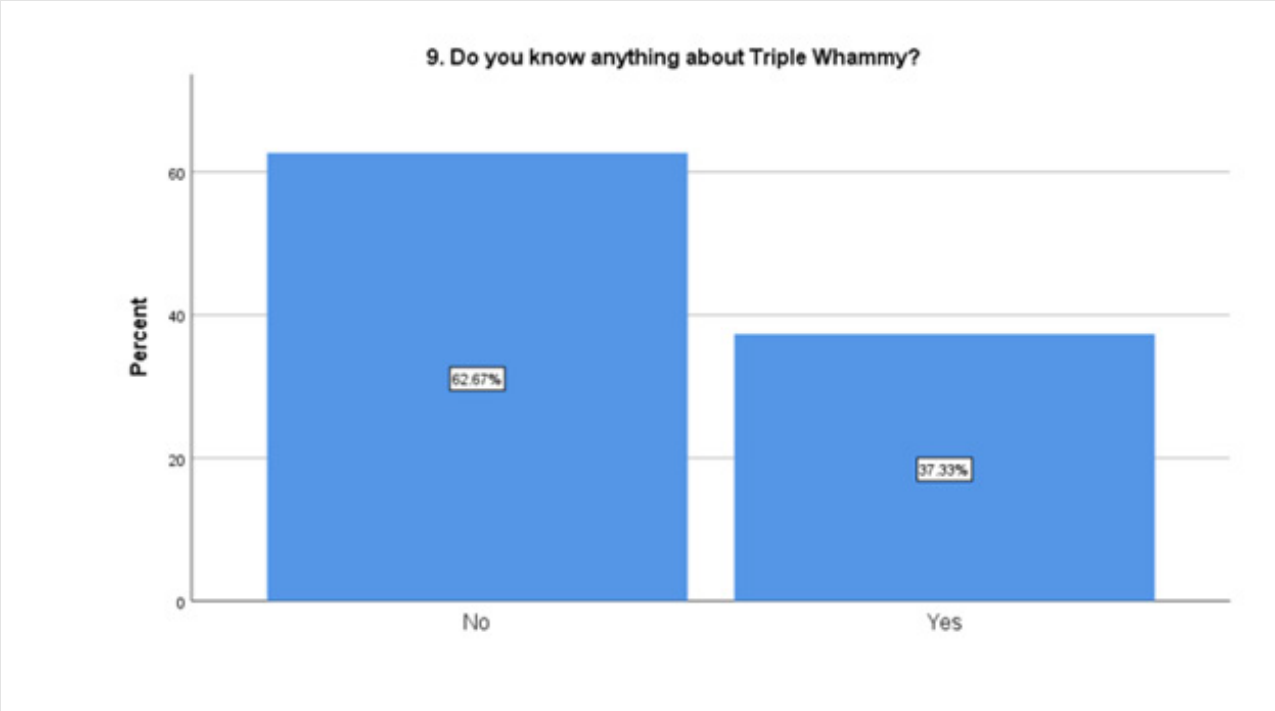

Figure 7: Bar chart showing knowledge about triple whammy.

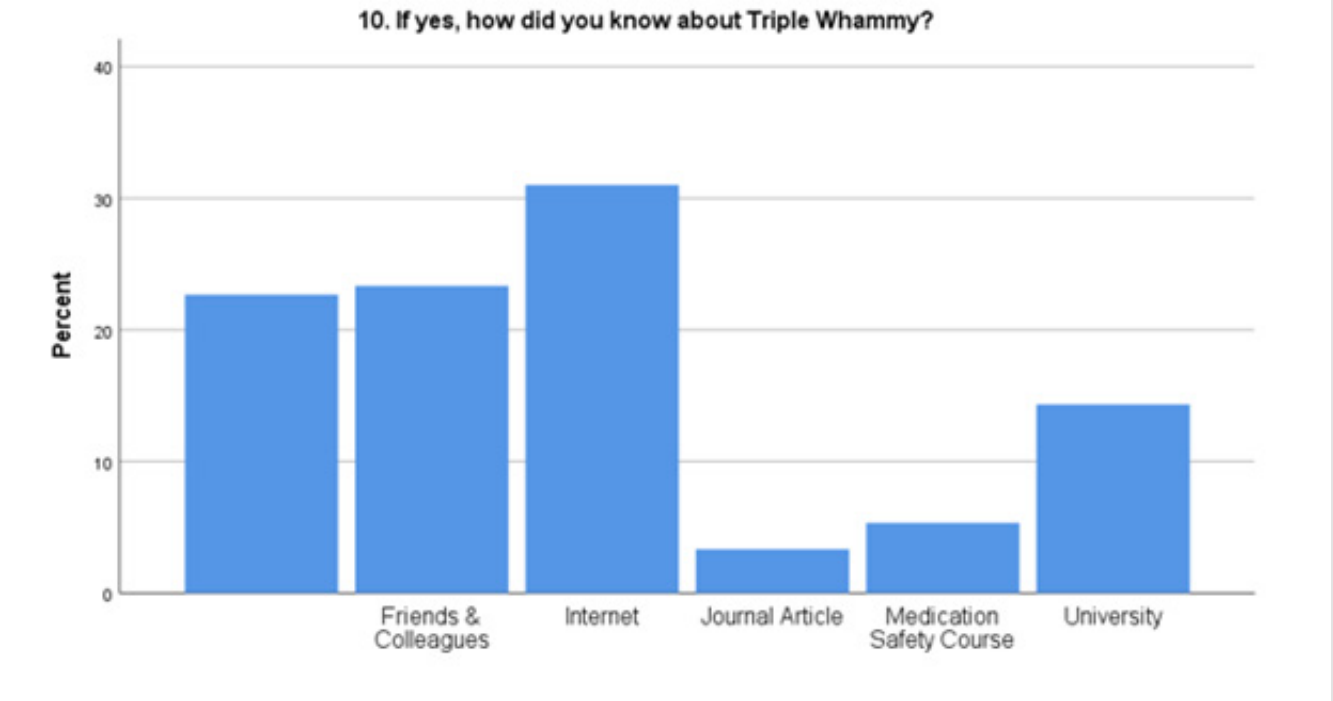

Figure 8: Bar chart showing source of triple whammy information.

Table 1: Demographics information.

1. Which category is your age?					
		Frequency	**Percent**	**Valid percent**	**Cumulative percent**
Valid	20 - 29	83	27.7	27.7	27.7
	30 - 39	185	61.7	61.7	89.3
	40 - 49	29	9.7	9.7	99
	50 - 60	3	1	1	100
	Total	300	100	100	

Table 2: Nationality.

1. What is your nationality?					
		Frequency	**Percent**	**Valid percent**	**Cumulative percent**
Valid	Non-Saudi	13	4.3	4.3	4.3
	Saudi	287	95.7	95.7	100
	Total	300	100	100	

Table 3: Organization of work.

1. Which organization do you work for?					
		Frequency	**Percent**	**Valid percent**	**Cumulative percent**
Valid	Community Pharmacy	28	9.3	9.3	9.3
	Primary Healthcare Centre (Public)	50	16.7	16.7	26
	Private Hospital	10	3.3	3.3	29.3
	Public Hospital Pharmacy	212	70.7	70.7	100
	Total	300	100	100	

Table 4: Triple whammy prescription.

1. Have you ever had prescription(s) containing two or more of Triple Whammy causing medications (ACEIs/ ARBs, diuretics and / or NSAIDs)?					
		Frequency	**Percent**	**Valid percent**	**Cumulative percent**
Valid	May be	148	49.3	49.3	49.3
	No	44	14.7	14.7	64
	Yes	108	36	36	100
	Total	300	100	100	

Table 5: Number of triple whammy prescription.

1. If yes, how many prescriptions did you have?					
		Frequency	**Percent**	**Valid percent**	**Cumulative percent**
Valid	5-Jan	21	7	7	7
	10-May	71	23.7	23.7	83.3
	15-Oct	107	35.7	35.7	42.7
	15-20	14	4.7	4.7	59.7
	> 20	71	23.7	23.7	83.3
	Total	300	100	100	

Table 6: Action for triple whammy.

7. What did you do when you had such prescription?					
		Frequency	**Percent**	**Valid percent**	**Cumulative percent**
Valid	Call the doctor and discuss the issue	97	32.3	32.3	32.3
	Dispensed it	94	31.3	31.3	63.7
	Report the prescription to the medication safety officer	40	13.3	13.3	77
	Send the patient back to the doctor	69	23	23	100
	Total	300	100	100	

Discussion

High percentage of our participating don`t know about Triple Whammy in about 62.7% but still the percentage of pharmacists know about Triple Whammy is 37% this is reflecting there is highly needed to make educational program to increase the knowledge about Triple Whammy. Internet and medical journal still had the best option to KSA to get the clinical information for any drugs and diseases the percentage of about 34.3 % comparing to friends the percentage 23.3% but the university about 14.3% this is indicating the need to increase the clinical education in regarding to triple whammy. There is a shortage in knowledge in triple whammy either between physician and pharmacists and either the patient because the percentage of prescription that containing Triple Whammy causing medications 36 % and these people is risky to some kidney injury this is reflecting there is high need to stress on this problem not only the pharmacists but also the physician and community.

Repeating prescriptions that are containing Triple Whammy causing medications is high and may reach more than 20 times in some situations. Our participating when they saw any prescription containing Whammy causing medications varying in their action but there still some of them not do report the error in the medication safety office this is needed to give more effort between quality and patient safety in this hospital to reporting these events to prevent more injury to the patients. Most of our participating not have any medication management system that alerts you about Triple Whammy causing interaction between ACEIs/ARBs, diuretics, and/or NSAIDs about 74.4 % this gives us more idea about the future planning in continues medical education to pharmacists Our participating give more solution to prevent like these error like Alert system by computerized, Applying continuous educational programs for pharmacists about most common issues related to medications errors, Awareness programs more investigation and studies are needed to judge the sensitivity and specificity of these solutions.

Conclusion

Treatment with ACEI, ARB-II, diuretics and/or NSAIDs shows a high incidence of hospitalization episodes due to AKI (Rosa Maria Garcia Camin, et al. [6]), males more common to participate in this study, the percentage was 65% and females about 35%. Non-Saudi pharmacists are participating in this study about 4.3% but the Saudi participating about 95.7 %. Most of the pharmacists are working in the field of pharmacy in KSA had a bachelor's degree in the pharmacy 65.3 % master's degree 15.3 % and Ph.D. only 1.7%, most our participating don`t know about Triple Whammy in about 62.7% and who know about this is 37%. Internet and medical journal still had the best option to KSA to get the clinical information for any drugs and diseases the percentage of about 34.3 % comparing to friends the percentage 23.3% but the university about 14.3% this is indicating the need to increase the clinical education in regarding to triple whammy. the percentage of pharmacists do not know anything about Triple Whammy in KSA is large 37% there is highly needed to make continuous medical education to increase the knowledge of pharmacists about the problem of combination of these drugs, some solution Was given by the pharmacists need to be more investigated.

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