

ORIGINAL ARTICLE

Suspected Captopril-Associated Adverse Drug Reactions among Hypertensive Patients: A Prospective Study in a Primary Healthcare Setting

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ABSTRACT

Adverse Drug Reactions (ADRs) are unintended and harmful responses to medicines occurring at doses normally used for disease prevention, diagnosis, or treatment. Hypertension is a chronic condition requiring long-term pharmacological therapy, and captopril, an Angiotensin-Converting Enzyme (ACE) inhibitor, is commonly used as an antihypertensive agent. This study aimed to determine the incidence and classification of ADRs and examine the association between sociodemographic characteristics, captopril treatment patterns, and the occurrence of captopril-related ADRs among hypertensive patients. This prospective observational study employed a cross-sectional assessment, with data collected prospectively through patient interviews from March to May 2024 at Andalas Community Health Center, Padang City, Indonesia. The Naranjo Algorithm was used to assess the probability of a causal relationship between captopril use and suspected ADRs. Ethical approval was obtained from the Faculty of Pharmacy, Universitas Andalas (No. 39/UN16.10.D.KEPK-FF/2024). Of the 44 patients receiving captopril therapy, 22 (50.0%) experienced at least one suspected ADR, with a total of 26 suspected ADR events identified. Dry cough was the most frequently reported ADR (69%), followed by dizziness (11%) and nausea (8%), swollen gums (4%), frequent urination (4%), and flatulence (4%). Based on the Naranjo Algorithm, 73% of ADRs were classified as probable and 27% as possible. No significant associations were found between sociodemographic characteristics or captopril treatment patterns and ADR occurrence ($p > 0.05$). Suspected ADRs were relatively common among patients receiving captopril, with dry cough being the most frequently reported reaction.

Keywords: hypertension; captopril; side effect; naranjo algorithm

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Article History:

Received: 17 Aug 2026

Revised: 09 Sep 2026

Accepted: 03 Oct 2026

DOI:

[https://doi.org/10.25077/jsfk.13.02.](https://doi.org/10.25077/jsfk.13.02.211-220.2026)

211-220.2026

Citation:

Yosmar R, Salsabila S, Almasdy D.
Suspected Captopril-Associated
Adverse Drug Reactions among
Hypertensive Patients: A Prospective
Study in a Primary Healthcare
Setting. *J Sains Farm Klin.*
2026;13(2):211-220

INTRODUCTION

Hypertension is one of the most prevalent chronic diseases worldwide. A significant increase in blood pressure is a risk factor for cardiovascular disease [1]. Hypertension is diagnosed when systolic pressure is ≥ 140 mmHg and/or diastolic pressure is ≥ 90 mmHg in repeated measurements. The development of hypertension is multifactorial, involving complex interactions among genetic predisposition, lifestyle and environmental factors, obesity, and sex-related factors [2]. According to the World Health Organization (WHO), the global prevalence of hypertension was alarmingly high at 22.1% (affecting 1.3 billion people) in 2019, rising to 30% in 2020 [3,4].

Data from the 2018 Basic Health Research (RISKESDAS) in Indonesia indicates that hypertension affected approximately 45.3% of individuals aged 45-54, 55.2% of those aged 55-64, 63.2% of those aged 65-74, and 69.5% of those aged 75 and older [5]. The 2022 Health Profile report for Padang City shows a hypertension prevalence of 22.4%, with more women affected (21,748 cases) compared to men (15,263 cases). The highest number of hypertension cases among individuals over 15 years old in Padang City was recorded in the Andalas Community Health Center area, totaling 14,161 patients in 2022 [6]. The high prevalence of hypertension underscores the importance of effective and safe long-

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term antihypertensive therapy, which provides the context for examining the use and safety of commonly prescribed agents.

Hypertension requires long-term pharmacological treatment to achieve and maintain adequate blood pressure control. Current guidelines recommend several major antihypertensive drug classes as first-line treatment, including angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers, dihydropyridine calcium channel blockers, and thiazide or thiazide-like diuretics [7]. Captopril, an ACE-I, is used in the management of hypertension and has been reported among antihypertensive medicines used in primary healthcare settings in Indonesia [8,9].

Although ACE-Is are generally well tolerated and effective in reducing blood pressure, their use may be associated with Adverse Drug Reactions (ADRs), which are negative and unintended reactions to a drug occurring at doses commonly used for prevention, diagnosis, treatment, or modification of physiological functions, particularly dry cough [7,10]. ACE inhibition reduces the degradation of bradykinin and other vasoactive peptides, which may increase airway sensitivity and contribute to the development of a persistent, non-productive cough [8,11]. However, the precise mechanism of ACE-I-induced cough remains incompletely understood and may involve multiple pathways. Consequently, monitoring for suspected ADRs is important during long-term antihypertensive therapy, particularly among patients receiving captopril [11,12].

Another Drug Related Problems is Drug Drug interaction (DDI), based on the study of Permata et al, there is a high prevalence of potential drug interaction in CHF patients, particularly interaction involving pharmacodynamic mechanisms, most of which were of moderate severity. They found a significant relationship between the average daily use of cardiovascular drugs and the potential for drug interactions ($p < 0.05$), while there is no significant relationship between the severity level of drug interactions and the clinical symptoms and signs of patients ($p > 0.05$) [13].

According to a 2018 study by Diatmika et al., 87% of patients experienced adverse effects from captopril, with the most common symptoms being dry cough

(76%), dizziness (50%), dry mouth (30%), constipation (12%), itchy spots (8%), indigestion (6%), and the least common being skin redness (4%) [14]. Jackson et al. reported 11 patients who developed adverse effects during captopril therapy, including proteinuria, skin rash, and taste disturbances. These reactions improved or resolved after captopril was replaced with enalapril, supporting a possible association between captopril use and these suspected ADRs [15].

Although previous studies have reported various adverse reactions to captopril, evidence on suspected captopril-associated adverse drug reactions (ADRs) in primary healthcare settings, particularly in Indonesia, remains limited. Most available studies have focused on specific ADRs or different patient populations and healthcare settings. In addition, limited information is available on the occurrence and probability classification of suspected ADRs and their association with patients' sociodemographic characteristics and captopril treatment patterns. This gap highlights the need for further evaluation of captopril-associated ADRs in primary care. Therefore, this study aimed to determine the occurrence and classification of suspected captopril-associated ADRs and to examine their association with sociodemographic characteristics and captopril treatment patterns among hypertensive patients at a community health center in Padang, Indonesia.

METHODS

Research design

This quantitative observational study was conducted at the Diabetes Mellitus/Hypertension (DM/HT) Polyclinic of Andalas Community Health Center, Padang, Indonesia, from March to May 2024. Data were collected prospectively through direct patient interviews using a structured data collection form. The Naranjo Algorithm was subsequently applied to assess the probability of a causal relationship between captopril use and suspected adverse drug reactions (ADRs). Participants were recruited during routine outpatient visits throughout the study period using an accidental sampling approach. Patients who met the predefined inclusion and exclusion criteria and were available during the data collection period were invited

to participate. After providing informed consent, eligible participants were interviewed directly by the researcher using a structured data collection form. Data collection continued throughout the three-month study period until its completion.

Patient criteria

Participants were eligible if they were adults (≥ 18 years) diagnosed with hypertension, had received antihypertensive therapy for at least one month, and were receiving captopril either as monotherapy or in combination with other antihypertensive agents. Additional eligibility criteria included having no complications or comorbidities, attending the Andalas Community Health Center during the study period, being able to communicate effectively, and providing written informed consent. Patients who were unable to complete the interview, provide sufficient information for suspected ADR assessment, or withdrew from the study were excluded.

A minimum treatment duration of one month was required to ensure adequate exposure to captopril and sufficient opportunity for the occurrence and recognition of suspected Adverse Drug Reactions (ADRs) during routine therapy. This threshold was established as an operational eligibility criterion and should not be interpreted as indicating that captopril-associated ADRs develop only after one month of treatment. Then, for patients receiving combination therapy, concomitant medications were considered as potential alternative causes during the assessment of suspected ADRs using the Naranjo Algorithm. Therefore, the identified events were reported as suspected captopril-associated ADRs rather than definitively attributed to captopril. In addition, in patients receiving combination antihypertensive therapy, the potential contribution of each antihypertensive medication was evaluated, with concomitant medications considered as potential alternative causes during the Naranjo causality assessment [16].

Causality Assessment Tool

The Naranjo Algorithm was used to assess the probability of a causal relationship between captopril use and suspected ADRs, which were classified as

definite, probable, possible, or doubtful [16,17].

Data Analysis

The occurrence of suspected adverse drug reactions (ADRs) was assessed using descriptive and inferential statistics. Categorical variables were summarized as frequencies and percentages. The primary outcome was the occurrence of suspected ADRs at the patient level, with patients categorized as either having experienced at least one suspected ADR or having experienced no suspected ADR during captopril therapy. The total number of suspected ADR events was also recorded and presented descriptively, as individual patients could experience more than one ADR.

Associations between sociodemographic characteristics, treatment patterns, and the occurrence of suspected ADRs were evaluated using the Chi-square test or Fisher's exact test, as appropriate. Fisher's exact test was applied when the expected cell frequencies were insufficient to satisfy the assumptions of the Chi-square test. Crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to estimate the strength and precision of the associations between age, gender, treatment pattern, and the occurrence of suspected ADRs. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 29.

Ethical approval

This study fully complies with national and international ethical standards in accordance with the Declaration of Helsinki. Ethical approval was granted by the Research Ethics Committee of the Faculty of Pharmacy, Universitas Andalas, Padang, under Protocol Registration Number 39/UN16.10.D.KEPK-FF/2024.

RESULT AND DISCUSSION

The Indonesian Ministry of Health (2019) reports that the prevalence of hypertension in women rises after they enter menopause. After the age of 65, women are at a higher risk of developing hypertension compared to men, primarily due to hormonal changes [18,19]. During a woman's reproductive years, hormonal conditions help maintain the elasticity of blood vessels. However,

Table 1. Patients Characteristic

Patients characteristic	n	Percentage [%]
Age		
Adult [19-59 y]	20	45
Elderly [≥60 y]	24	55
Gender		
Man	5	11
Woman	39	89
Treatmen Pattern		
Single [Captopril]	16	36
Combination [Captopril + Amlodipine]	28	64

as menopause approaches, this elasticity decreases, contributing to the development of systolic hypertension and heart failure [18]. **Table 1** shows that female patients accounted for 89% of the study population. This finding is consistent with previous studies in Indonesia reporting a higher prevalence of hypertension among women than men, including 52.3% versus 43.1% among adults aged ≥40 years and 35.4% versus 31.0% in a national population-based survey. However, the predominance of female patients in the present study should be interpreted as a characteristic of the study population rather than as evidence of a higher risk of captopril-induced adverse drug reactions among women [20,21].

The Fisher test analysis between gender and the incidence of ADR showed a p-value of 0.500, indicating the relationship is not statistically significant between gender and the occurrence of ADR due to captopril. These findings are consistent with research by Halim et al. (2015), which also found no significant link between gender and the incidence of dry cough caused by ACE inhibitors [22]. Similarly, Alhawassi et al. (2018) reported no significant association between female gender and an increased risk of ADR in hypertensive patients [23].

The Indonesian Ministry of Health (2019) states that as individuals age, the risk of developing hypertension increases [19]. This is due to physiological changes that lead to higher systolic blood pressure, arterial pressure, pulse pressure, and a reduced ability to adapt to hemodynamic shifts. Aging affects the vascular system, heart, and autonomic nervous system [24]. Liao

et al (2017) also found that hypertension risk in elderly patients is linked to decreased systolic elasticity in the atria, causing stiffness. As a result, with each heartbeat, blood is forced through narrower vessels, leading to elevated blood pressure [25]. In this study, the majority of hypertensive patients were elderly (≥60 y). The Chi-square test showed no significant association between patient age and the occurrence of suspected ADRs ($p = 0.131$). This finding is consistent with research by Halim et al. (2015), which reported no significant association between patient age and the incidence of dry cough from ACE inhibitors [22]. Additionally, research by Azimivaghar and Javadirad (2014) suggested that the incidence of cough due to captopril may decrease with increasing age [26].

Among the 44 patients included the inclusion criteria, 16 received captopril as a single antihypertensive treatment, while 28 were treated with a combination of captopril and amlodipine. Captopril belongs to the ACE inhibitor (ACE-I) class, which is considered a first-line treatment for hypertension. ACE inhibitors work by blocking the Angiotensin Converting Enzyme, thereby preventing the conversion of angiotensin I to angiotensin II. This inhibition results in vasodilation and a reduction in aldosterone levels [27]. Current hypertension guidelines recommend angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium channel blockers (CCBs) among the first-line antihypertensive drug classes. When blood pressure control is not adequately achieved with monotherapy, combination therapy involving agents with complementary mechanisms of action may be considered to enhance blood pressure reduction [7,8].

In the present study, the use of captopril in combination with amlodipine may therefore reflect an approach to achieving more effective blood pressure control. Captopril inhibits the renin-angiotensin-aldosterone system by reducing the formation of angiotensin II, resulting in vasodilation and reduced aldosterone-mediated sodium and water retention. In contrast, amlodipine, a dihydropyridine CCB, inhibits calcium influx into vascular smooth muscle cells, thereby producing peripheral arterial vasodilation. The combination of these agents provides antihypertensive effects through distinct but complementary mechanisms

and may consequently enhance overall blood pressure reduction [7].

The predominance of combination therapy in this study is also important when interpreting suspected adverse drug reactions (ADRs). Patients receiving captopril and amlodipine were exposed to two antihypertensive agents; therefore, an adverse event cannot be attributed exclusively to captopril solely on the basis of its occurrence during treatment. Accordingly, the findings should be interpreted as suspected captopril-associated ADRs rather than definitive captopril-induced ADRs. Causality assessment using the Naranjo algorithm can help estimate the probability of a causal relationship, although the results should be interpreted in conjunction with the patient's clinical characteristics, concomitant medications, and other potential causes of the reported event. This consideration is particularly relevant in routine clinical practice, where polypharmacy may complicate the attribution of suspected ADRs to individual medications [16,28].

The Chi-Square test analysis for the relationship between treatment patterns and the incidence of ESO yielded a value of 0.210, indicating no significant relationship between antihypertensive treatment patterns and drug side effects due to captopril. This finding aligns with research by Alhawassi et al. (2018), which found no significant link between the number of medications taken by patients and the increased risk of ESO in hypertensive patients [23]. In contrast, Palikhey et al. (2022) reported that combination therapy is associated with a higher incidence of drug side effects, with a Chi-Square value of 0.001, indicating a very significant relationship. Combination therapy can increase the risk of side effects due to potential drug interactions. Therefore, it is advisable in hypertension management to prescribe only the necessary medications to minimize the risk of interactions in combination therapy [29].

Amlodipine is a long-acting dihydropyridine calcium channel blocker (CCB) commonly used in the management of hypertension. CCBs inhibit the influx of calcium through L-type calcium channels in vascular smooth muscle, thereby reducing vascular contraction and promoting arterial vasodilation. This drug class is

broadly divided into dihydropyridines and nondihydropyridines. Dihydropyridines, including amlodipine, primarily exert their effects on vascular smooth muscle, whereas nondihydropyridines, such as verapamil and diltiazem, have more pronounced effects on cardiac conduction and contractility. Although vasodilation caused by dihydropyridine CCBs may induce reflex tachycardia, this response is generally less prominent with amlodipine because of its gradual onset of action. CCBs are also considered effective options for treating hypertension in older adults, particularly those with isolated systolic hypertension, although treatment selection should be individualized according to comorbidities, tolerability, and the patient's overall clinical condition [30,31]

The adverse-effect profile of amlodipine is primarily related to its vasodilatory action. Peripheral edema, particularly in the ankles and lower limbs, is one of the most characteristic adverse effects. It occurs mainly because of preferential dilation of precapillary arterioles, which increases capillary hydrostatic pressure and promotes the movement of fluid into the interstitial space. Consequently, amlodipine-associated edema is not primarily caused by sodium and water retention. The risk of peripheral edema is also dose-dependent and may be greater with higher doses. In a meta-analysis of randomized controlled trials, peripheral edema occurred more frequently with amlodipine than with placebo (16.6% vs. 6.2%), with a relative risk of 2.9 [32]

Other reported adverse effects include dizziness, headache, flushing, and hypotension. Dizziness and hypotension may result from excessive reductions in blood pressure or vasodilation, particularly during treatment initiation or dose escalation. Flushing is associated with increased cutaneous blood flow following peripheral vasodilation, whereas headache may occur as a consequence of vascular changes. These reactions are generally mild to moderate, although their occurrence may affect treatment tolerability and adherence. The incidence of several adverse effects, including edema, dizziness, and flushing, may increase with higher doses of amlodipine [30,32].

This study utilized the Naranjo Algorithm to assess whether the ADRs experienced by patients were

Table 2. The Number of Patients Who Experienced suspected ADR

Variables	n	Percentage [%]
Experienced suspected ADR	22	50
Not experienced suspected ADR	22	50
Total Patients	44	100

truly caused by captopril or other factors. The algorithm consists of 10 questions with "Yes," "No," or "Don't know/Not done" responses, each assigned different values. It classifies the causality into four categories: definite, probable, possible, and doubtful. Among the 22 patients who experienced ADRs, 19 cases fell into the "probable" category, indicating that the drug was most likely responsible, while 7 cases were categorized as "possible," meaning the drug's involvement was uncertain. The analysis concluded that the minimum acceptable category for attributing side effects to the drug is "probable," accounting for 73%.

Among the 44 patients receiving captopril therapy, 22 patients (50%) experienced at least one suspected ADR (Table 2). A total of 26 suspected ADR events were identified, indicating that some patients experienced more than one type of suspected ADR. Thus, the number of patients experiencing ADRs ($n = 22$) differs from the total number of ADR events ($n = 26$). The data from the Table 3 shows that the most common suspected ADRs events is a dry cough accounted for 18 of the 26 suspected ADR events (69%). This finding aligns with previous studies, including research by Manik et al. (2023)

conducted at a pharmacy in Medan City from June to July 2022, where dry cough was reported in 83.33% of cases [33]. Another study by Diatmika et al. (2018) at the East Denpasar Health Center in 2017 also found that dry cough was the most frequent suspected ADRs among patients using captopril, occurring in 76% of cases [14].

According to DiPiro (2017), dry cough is a common ADR in patients using ACE inhibitors [ACE-I] for hypertension. While this cough does not affect the respiratory tract, it can be bothersome to patients and may impact their adherence to medication [34]. The cough is caused by the inhibition of bradykinin conversion into inactive metabolites due to ACE-I use, leading to bradykinin accumulation [12]. This accumulation, along with increased stimulation of vagal afferent nerve fibers and inflammatory mediators like prostaglandins and substance P, contributes to the development of a dry cough in patients taking captopril [35].

Another ADR experienced by patients is dizziness (11%). This finding aligns with research by Diatmika et al. [2018], which reported that 50% of patients using captopril experienced dizziness [14]. The exact mechanism behind dizziness in patients using captopril is not fully understood. Dizziness was identified as one of the suspected ADRs in the present study. This finding is consistent with previous reports indicating that dizziness may occur during captopril therapy. In a large postmarketing surveillance study involving 30,515 patients receiving captopril, dizziness was reported in 1.6% of patients [36]. Similarly, transient postural dizziness has been reported following captopril

Table 3. Cases of Suspected ADR Due to Captopril Use

No	ADR	Score of Naranjo Algorithm				Total Cases [n=26]	Percentage [%]
		Definite	Probable	Possible	Doubtful		
1	Dry cough	0	15	3	0	18	69
2	Dizzines	0	2	1	0	3	11
3	Nausea	0	1	1	0	2	8
4	Swollen gum	0	0	1	0	1	4
5	Frequent urination	0	0	1	0	1	4
6	Flatulence	0	1	0	0	1	4
Total		0	19 [73%]	7 [27%]	0	26	100

administration in hypertensive patients [23]. The occurrence of dizziness may be related to the blood pressure-lowering effect of captopril, particularly when an excessive reduction in blood pressure occurs [24].

Nausea was reported by 2 patients (8%) among the suspected ADR events. However, its specific mechanism could not be established because no radiological evidence, specific clinical signs, or physician-confirmed diagnosis of intestinal angioedema was available. Furthermore, dechallenge or rechallenge was not performed. Therefore, nausea was reported as a suspected captopril-associated ADR based on the Naranjo Algorithm, rather than as a confirmed captopril-induced reaction [8,37].

Other less frequently reported suspected ADR events included frequent urination (4.0%), swollen gums (4.0%), and flatulence (4.0%), with each event reported by one patient. Because these symptoms were based on patient-reported information and were not supported by objective clinical measurements, they should be interpreted as suspected ADRs rather than confirmed captopril-induced reactions. The possibility of alternative causes, including concomitant medications, should also be considered [8,38].

Based on the data shown in **Table 4**, the proportion of patients experiencing suspected ADRs was higher in

the adult group than in the older adult group. Compared with adults as the reference category, older adults had an OR of 0.40 (95% CI: 0.12–1.33; $p = 0.131$). This estimate suggests that the odds of experiencing a suspected ADR were approximately 60% lower among older adults than among adults. However, this association was not statistically significant, as the p -value exceeded 0.05 and the 95% CI included the null value of 1. For male patients, the odds of experiencing a suspected ADR were approximately 37% lower than those among female patients (OR = 0.63). However, the 95% confidence interval (CI: 0.10–4.22) included the null value of 1, indicating that there was insufficient evidence of a statistically significant association between gender and the occurrence of suspected ADRs ($p = 1.000$).

The wide confidence interval should be interpreted with caution, as the male group comprised only five patients, of whom two experienced suspected ADRs and three did not. This small subgroup size likely contributed to the substantial uncertainty surrounding the OR estimate and, consequently, its limited precision. Among patients receiving captopril monotherapy, 10 of 16 patients (62.5%) experienced suspected ADRs, compared with 12 of 28 patients (42.9%) receiving combination therapy with captopril and amlodipine. Thus, descriptively, suspected ADRs were more

Table 4. Association between patient characteristics, captopril treatment patterns, and the occurrence of suspected ADRs

Total Patients [n=44]						
No	Variables		Experienced suspected ADR n (%)	Not experienced suspected ADR n (%)	Total	OR (95% CI) p-value
1	Age	Adult [19-59 y]	13 (61.9)	8 (38.1)	21	Reference
		Elderly [≥ 60 y]	9 (39.1)	14 (60.9)	23	0.40 (0.12-1.33) 0.131 ^a
2	Gender	Female	20 (51.3)	19 (48.7)	39	Reference
		Male	2 (40)	3 (60)	5	0.63 (0.10-4.22) 1.000 ^b
3	Treatment Pattern	Single [Captopril]	10 (62.5)	6 (37.5)	16	Reference
		Combination [Captopril + Amlodipine]	12 (42.9)	16 (57.1)	28	0.45(0.13-1.58) 0.210 ^a

Notes :

a : Chi-square Test

b : Fisher exact Test

frequently observed among patients receiving captopril monotherapy. Compared with captopril monotherapy, combination therapy was associated with an OR of 0.45 (95% CI: 0.13–1.58; $p = 0.210$). This indicates that the odds of experiencing a suspected ADR were approximately 55% lower among patients receiving combination therapy than among those receiving captopril monotherapy. However, this association was not statistically significant, as the p -value was greater than 0.05 and the confidence interval included 1.

This study evaluated suspected Adverse Drug Reactions (ADRs) associated with captopril therapy among hypertensive patients, focusing on their occurrence, probability of causality based on the Naranjo Algorithm, and associations with patient characteristics and treatment patterns. Prospectively collected data were obtained through patient interviews, and suspected ADRs were assessed using the Naranjo Algorithm. The findings provide information on the types and occurrence of suspected ADRs during captopril therapy and may contribute to increased awareness of ADR monitoring among healthcare professionals and pharmacists in primary healthcare settings. These findings may also have potential implications for the early identification and appropriate management of suspected ADRs, thereby supporting patient safety and continuity of pharmacotherapy. However, these potential implications were not directly evaluated in this study.

Several limitations should be considered when interpreting the findings. Items 3, 4, 6, 7, and 8 of the Naranjo Algorithm could not be adequately assessed because the information required to answer these items was unavailable, resulting in a score of 0 for each item. In addition, complete case-report information was not always available, and the number of patients receiving captopril in combination with other antihypertensive medications was limited. Consequently, the findings should be interpreted cautiously, particularly with respect to the causal attribution of suspected ADRs to captopril.

CONCLUSION

Suspected Adverse Drug Reactions (ADRs) were identified in 22 of the 44 patients (50%) receiving captopril therapy, corresponding to 26 suspected ADR events. According to the Naranjo Algorithm, 19 events (73%) were classified as probable and 7 (27%) as possible. No statistically significant associations were observed between the occurrence of suspected ADRs and the patients' sociodemographic characteristics or captopril treatment patterns (all $p > 0.05$). These findings suggest that suspected ADRs were relatively common among patients receiving captopril therapy and underscore the potential importance of routine monitoring to facilitate their early identification and appropriate management during long-term antihypertensive treatment.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

ACKNOWLEDGEMENT

The authors extend their gratitude to individuals who contributed substantially to this study. Especially the Faculty of Pharmacy Universitas Andalas and Andalas Community Health Center.

FUNDING

Source of research funding by research grant for beginner lecturers from RKAT Fund of the Faculty of Pharmacy, Universitas Andalas with contract no 23/UN16.10.D/PJ.01./2024

AUTHOR CONTRIBUTIONS

RY: Principal investigator, conceptualization, supervision, writing-original draft and data analysis; SS: Data collection, writing-original draft and data analysis, DA: Supervision, conceptualization and review. All authors approved the final version of the manuscript.

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