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Research Article

Evaluation of Apatinib-Related Hypertension and Identification of Clinical Risk Factors

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Purpose. Hypertension (HTN) is one of the most common adverse drug reactions to tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor (VEGF), but little is known about its clinical risk factors. The aim of this study was to elucidate the association between baseline clinical characteristics and the occurrence of HTN in advanced gastric cancer (GC) patients prescribed apatinib, a commonly used VEGF-TKI in China, in a real-world setting. *Patients and Methods*. Fifty-five GC patients treated with apatinib from December 1st, 2016, to December 1st, 2020, were retrospectively included in electronic medical records. Adverse drug reactions were defined according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Univariate and multivariable logistic regression analyses were used to investigate potential clinical risk factors for apatinib-related HTN. *Results*. The incidence of apatinib-related HTN of all grades was 45.45%, and grade 3 HTN occurred in 16.36% of patients. The median maximal systolic blood pressure (SBP) during apatinib treatment was 153 mm·Hg, and the median time to event was 25 days. New-onset HTN occurred in 10/33 (30.30%) patients. Preexisting HTN (odds ratio [OR]: 4.155; 95% confidence interval [CI]: 1.252, 13.787; $p = 0.020$) was the key independent risk factor associated with apatinib-related HTN. *Conclusion*. The incidence of HTN was high in patients treated with apatinib, and preexisting HTN was an independent risk factor. It is important to provide thorough and close monitoring of patients during treatment with apatinib, especially for those with preexisting HTN. This trial is registered with ChiCTR1900024531.

1. Introduction

A preprint has previously been published [1]. Angiogenesis is a rate-limiting step in many pathologic processes, including malignant tumor growth [2]. VEGF, as a major growth factor regulating angiogenesis, plays a critical role in the occurrence and development of tumors [3]. The importance of vascular endothelial growth factor receptor 2 (VEGFR-2) signaling as a therapeutic target in advanced or metastatic gastric cancer was confirmed in a phase III trial, which demonstrated a modest but significant survival benefit for the VEGFR-2 inhibitor apatinib after progression on second-line chemotherapy [4]. In China, approximately 396,500 patients are diagnosed with GC each year [5]. According to the data from the National Cancer Center (NCC) of China, the average age at diagnosis of GC was 67.35 years [6], and many of the patients were at increased risk or had preexisting cardiovascular disease prior to initiation of anti-VEGF therapy.

Apatinib mesylate (YN968D1, Shanghai Hengrui Pharmaceutical Co., Ltd. (Shanghai, China)), is an oral small-molecule-targeted VEGF receptor TKI that potently suppresses the kinase activities of VEGFR-2, c-kit, and c-src and inhibits the cellular phosphorylation of VEGFR-2, c-kit, and PDGFRβ [7]. Apatinib was approved by the National Medical Products Administration (NMPA) of China for the treatment of adenocarcinoma of the stomach or adenocarcinoma of the gastroesophageal junction in 2014 and hepatocellular carcinoma in 2020. More importantly, in a series of subsequent clinical studies, apatinib also showed significant survival benefits and good safety profiles in the treatment of multiple other tumors [8–10]. However,

hypertension (HTN), the most common adverse drug reaction to antiangiogenic inhibitors, is usually observed in VEGF/VEGFR inhibitors, which can cause secondary hypertension or aggravate preexisting hypertension [11, 12]. According to a phase III trial, the incidence of HTN (with any grade) was 46.4%, and the incidence of grade 3 or 4 HTN was 24.0% [4]. The mechanism of HTN in patients receiving anti-VEGF therapy remains unclear. Decreased nitric oxide (NO)/prostacyclin (PGI_2) secretion by endothelial cells/platelets, abnormal blood vessel density (small vessels and capillaries), vascular stiffness, and endothelin dysfunction may contribute to HTN [13–15].

The development of clinically important hypertension can lead to disease progression and apatinib dose reduction or discontinuation, thereby limiting the integrated efficacy of cancer therapy. The change in BP during treatment with apatinib has not been well characterized. In addition, the occurrence of treatment-related hypertension is frequent, but clinical risk factors for the development of hypertension have rarely been reported. Therefore, we aimed to evaluate the characteristics of hypertension associated with apatinib and identify its clinical risk factors in GC patients in a real-world setting.

2. Material and methods

2.1. Trial Design. The study was conducted at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College in Beijing, China, and approved by the Institutional Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

The study was registered at the chinadrugtrials.org.cn identifier ChiCTR1900024531 (registered on 2019–7–14) and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

2.2. Study Participants. We retrospectively identified all patients treated with apatinib from December 1, 2016, to December 1, 2020, using electronic medical records (EMRs). Patients with histologically confirmed advanced or metastatic gastric or gastroesophageal junction adenocarcinoma by International Classification of Diseases-10 (ICD-10) diagnosis codes who underwent at least two follow-up visits during apatinib therapy were included. Patients were excluded if apatinib therapy was stopped within 28 days after initiation if the medical record was not complete or if BP data were missing. A total of 177 patients were excluded, and the remaining 55 patients formed the final cohort for this study (Figure 1).

Demographic and baseline data were collected from EMRs, including past medical history elements and medication lists provided at each oncologic-related visit. Baseline characteristics included sex, age at apatinib start date, body mass index (BMI), history of chronic disease, concomitant medications, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, number of metastatic sites, tumor node metastasis (TNM) classification, operation history, radiotherapy history, starting dose of apatinib, dose adjustments, and reasons. Validation by manual chart review of patient medication lists and providers' documentation in the EMR was performed for each patient to ensure the accuracy of all the data.

2.3. Hypertension Data Review. Baseline systolic (S) and diastolic (D) BP were defined as the mean of each patient's blood pressure at each hospitalization 90 days prior to initiation of apatinib treatment. SBP and DBP following apatinib use were determined based on mean blood pressure measured at hospital visits of which there were at least two (one was at two weeks after apatinib initiation, and the other was at four weeks after initiation of treatment).

2.4. Definition of Preexisting Hypertension. The occurrence of apatinib-related HTN was the primary outcome of the study. Patients were considered to have preexisting HTN if they met any of the following criteria prior to initiation of apatinib treatment: (a) diagnosis of HTN in EMR; (b) at least one antihypertensive drug recorded in the EMR; (c) on the basis of National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v5.0) [16] and Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC) [17], SBP ≥ 140 mm·Hg or DBP ≥ 90 mm·Hg on the average of two or more properly measured, seated, BP readings at each of two or more hospital visits before initiation of apatinib treatment.

2.5. Definition of Apatinib-Related Hypertension. Patients were considered to have apatinib-related HTN (with or without preexisting HTN) if they met any of the following criteria after initiation of apatinib treatment: (a) added a new antihypertensive drug and (b) increased dose of antihypertensive drugs. Classification of HTN was also defined according to CTCAE v5.0. Table 1 lists the definitions and severity of apatinib-related HTN.

2.6. Statistical Analysis. Continuous variables are summarized as the mean and standard deviation. If the distribution of a value is skewed, it is presented as the median and range (minimum and maximum values) or the interquartile range ((IQR): 25th–75th percentile). Categorical values are summarized with counts and percentages for each level of the variable [18] and were compared using the Chi-square test or Fisher's exact test as appropriate. The SBP and DBP measurements during treatment with apatinib relative to baseline BP were compared and analyzed with the covariance between the apatinib-related HTN and no apatinib-related HTN.

Univariate logistical regression analysis was performed using the forward LR method (forward stepwise regression method based on maximum likelihood estimation) to determine the risk factors for apatinib-related HTN. Occurrence or nonoccurrence of apatinib-related HTN was used as the dependent variable. Exploratory variables included sex,

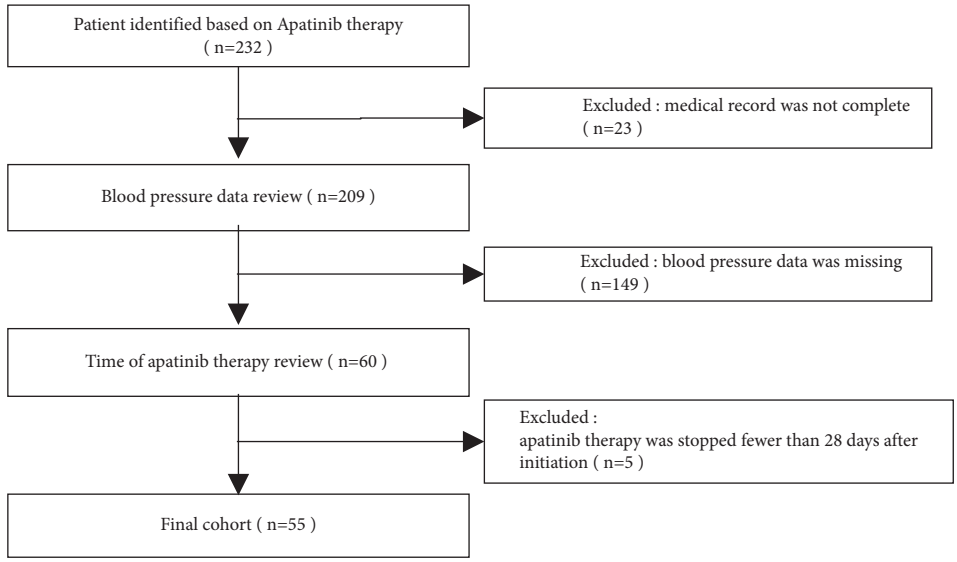

Figure 1: Inclusion/exclusion flow diagram.

Table 1: Definitions and severity of apatinib-related HTN.

Grade	Definition
Grade 1	Systolic BP 120–139 mm·Hg or diastolic BP 80–89 mm·Hg
Grade 2	Systolic BP 140–159 mm·Hg or diastolic BP 90–99 mm·Hg if previously within normal limits; change in baseline medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by > 20 mm·Hg (diastolic) or to >140/90 mm·Hg; monotherapy indicated
Grade 3	Systolic BP ≥ 160 mm·Hg or diastolic BP ≥ 100 mm·Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, and hypertensive crisis); urgent intervention indicated
Grade 5	Death

BP: blood pressure.

age, BMI, TNM classification, operation history, prior radiotherapy, smoking history, number of metastatic sites, starting dose of apatinib, preexisting HTN and diabetes, baseline SBP and DBP, ECOG PS, and concomitant medications. ORs with 95% CIs were generated. Statistical significance was set at p less than 0.05. All statistical analyses were performed using SPSS 22.0.0.0. After the identification of any clinical variables ($p < 0.050$), multivariable logistic regression was conducted to identify independent factors associated with the development of apatinib-related HTN.

3. Results

3.1. Patient Demographic and Baseline Characteristics. Between December 1, 2016, and December 1, 2020, 232 patients received apatinib at our hospital, of which 55 patients were included in the study. A total of 177 patients were excluded because they had only one visit or their EMRs had incomplete baseline data or BP measurements.

Patient demographic and baseline characteristics are summarized in Table 2. The study population analyzed statistically ($n = 55$) included 40 men (72.73%), and the median age was 59 years (range: 33–75 years). The majority of patients (83.09%) had stage IV GC. The ECOG-PS score was 0 or 1 in 85.45% and 2 or above in 14.55% of the patients. In total, 40.00% had hypertension, and 23.64% had diabetes mellitus. A total of 36.36% had a smoking history, 40.00% of the patients received a prior operation, and 5.45% received prior radiotherapy. The initial dose of apatinib ranged from 125 mg once daily to 850 mg once daily, and the majority of patients were started on a dose of apatinib 125~250 mg daily (61.82%).

3.2. Description of the Change in BP during Treatment with Apatinib. Compared to patients who did not develop apatinib-related HTN, patients in the apatinib-related HTN group had a higher mean baseline SBP (121.64 ± 10.77 mm·Hg vs. 119.53 ± 8.38, $p = 0.413$) and DBP (77.16 ± 7.59 mm·Hg vs. 76.63 ± 5.97, $p = 0.770$).

SBP and DBP were all adjusted according to the baseline blood pressure. The adjusted SBPs were associated with a significant increase ($F = 15.929$, $p < 0.001$) in apatinib-related HTN of 14.340 (95% CI: 9.157, 19.524) mm·Hg and an increase in no apatinib-related HTN of 0.341 (95% CI: −4.388, 5.070) mm·Hg. The adjusted DBPs were associated with a significant difference ($F = 5.093$, $p = 0.028$) in the apatinib-related HTN group of 7.948 (95% CI: 3.956, 11.941) mm·Hg and in the no apatinib-related HTN group of 1.867 (95% CI: −1.777, 5.511) mm·Hg (Table 3).

3.3. Description of Apatinib-Related HTN. In total, apatinib-related HTN occurred in 25/55 patients (45.45%), grade 3 HTN occurred in 9/55 patients (16.36%), and no patient experienced grade 4 or grade 5 HTN. The time to new onset of apatinib-related HTN was 25 days (IQR: 13–42 days). Among 22 patients with preexisting HTN, 15 met the criteria

Table 2: Patient demographic and baseline characteristics.

Patient characteristics	Total cohort ($N = 55$)	Apatinib-related HTN ($N = 25$)	No apatinib-related HTN ($N = 30$)	p value
Male gender	40 (72.73)	19 (76.00)	21 (70.00)	0.619
Age (years)	58.40 ± 10.05	59.84 ± 8.76	57.20 ± 11.02	0.332
BMI (kg/m^2)	22.69 ± 3.45	23.72 ± 3.36	21.82 ± 3.33	0.042*
TNM classification				0.204
III	6 (10.91)	1 (4.00)	5 (16.67)	
IV	49 (89.09)	24 (96.00)	25 (83.33)	
Prior operation	22 (40.00)	9 (36.00)	13 (43.33)	0.580
Prior radiotherapy	3 (5.45)	0	3 (10.00)	1.000
Smoker	20 (36.36)	5 (20.00)	15 (50.00)	0.959
Diabetes mellitus	13 (23.64)	7 (28.00)	6 (20.00)	0.487
Preexisting HTN	22 (40.00)	15 (60.00)	7 (23.33)	0.006*
ECOG PS				0.440
0	14 (25.45)	7 (28.00)	7 (23.33)	
1	33 (60.00)	13 (52.00)	20 (66.67)	
≥2	8 (14.55)	5 (20.00)	3 (10.00)	
Number of metastatic sites				1.000
0–2	51 (92.73)	23 (92.00)	28 (93.33)	
≥3	4 (7.27)	2 (8.00)	2 (6.67)	
Baseline SBP (mm·Hg)	120.49 ± 9.51	121.64 ± 10.77	119.53 ± 8.38	0.413
Baseline DBP (mm·Hg)	76.87 ± 6.70	77.16 ± 7.59	76.63 ± 5.97	0.772
Apatinib therapy				0.210
Initial dose 125–250 mg QD	34 (61.82)	13 (52.00)	21 (70.00)	
Initial dose 425–500 mg QD	20 (36.36)	11 (44.00)	9 (30.00)	
Initial dose 750–850 mg QD	1 (1.82)	1 (4.00)	0	

Data are presented as a number with percent (%) and mean ± standard deviation. *Demographic parameters are significantly different between study groups ($p < 0.050$). HTN: hypertension; QD: once daily; ECOG: Eastern Cooperative Oncology Group performance status; BP: blood pressure; BMI: body mass index.

Table 3: Description of systolic/diastolic blood pressure.

	Apatinib-related HTN	No apatinib-related HTN	F	Sig
Mean SBP change (mm·Hg) (95% CI)	14.340 (9.157, 19.524)	0.341 (−4.388, 5.070)	15.929	<0.001
Mean DBP change (mm·Hg) (95% CI)	7.948 (3.956, 11.941)	1.867 (−1.777, 5.511)	5.093	0.028

SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension.

for apatinib-related HTN. An antihypertensive drug was started or increased in dose in 22 patients. The majority of these were CCBs (68.18%) (Table 4). As shown in Figure 2, apatinib treatment resulted in a considerable rise in SBP and DBP from baseline to the maximum measurement, with a total median SBP and DBP after apatinib exposure of 13.83 mm·Hg and 7.82 mm·Hg higher than baseline, indicating SBP and DBP of the patients increased by 11.37% and 10.13%, respectively.

BMI (OR: 1.187; 95% CI: 1.003, 1.406; $p = 0.046$) and preexisting HTN (OR: 4.929; 95% CI: 1.538, 15.793; $p = 0.007$) were significant univariate predictors of the development of apatinib-related HTN. Multivariate analysis showed that preexisting HTN (OR: 4.155; 95% CI: 1.252, 13.787; $p = 0.020$) was a significant risk factor for the development of apatinib-related HTN (Table 5).

4. Discussion

Our study evaluated the risk factors for HTN in GC patients receiving apatinib in a retrospective study and analyzed all BPs measured at oncology clinics to quantify the changes in hypertension relative to baseline. This is the first study to exclusively examine apatinib-related hypertension in advanced GC patients in a clinical setting. This study demonstrated a high incidence of hypertension (all grade, 45.45%; grade 3, 16.36%) associated with apatinib in GC patients. The majority of apatinib-related HTNs were grade I or II, and high-grade hypertension could limit therapy and lead to other cardiovascular complications. Hypertension is one of the most common cardiovascular side effects of VEGF inhibitors, with reported rates ranging from 5 to 80% in a previous study [19]. In a meta-analysis including 7 prospective trials, 820 patients were treated with apatinib, and the incidences of all grade and grade 3 or 4 hypertension were 45.4% and 9.7%, respectively [20]. To prolong the survival time of cancer patients, improving the quality of life by reducing complications is meaningful and necessary. Hypertension is a risk factor for overall mortality and cardiovascular-specific fatal and nonfatal outcomes [21]. Therefore, it is important to recognize and manage apatinib-related HTN appropriately.

Table 4: Description of apatinib-related HTN.

Parameter	Apatinib-related HTN ($N = 25$)
SBP change (mm·Hg)	13.83 ± 17.69
DBP change (mm·Hg)	7.82 ± 11.47
Maximal SBP (mm·Hg)	153.24 ± 16.37
Maximal DBP (mm·Hg)	95.20 ± 13.18
Classification of antihypertensive started or intensified n (%)	22 (88.00)
Calcium-channel blockers	15 (68.18)
Beta-blockers	4 (18.18)
Diuretics	3 (13.64)

Data are presented as a number with percent (%). SBP: systolic blood pressure; DBP: diastolic blood pressure; HTN: hypertension.

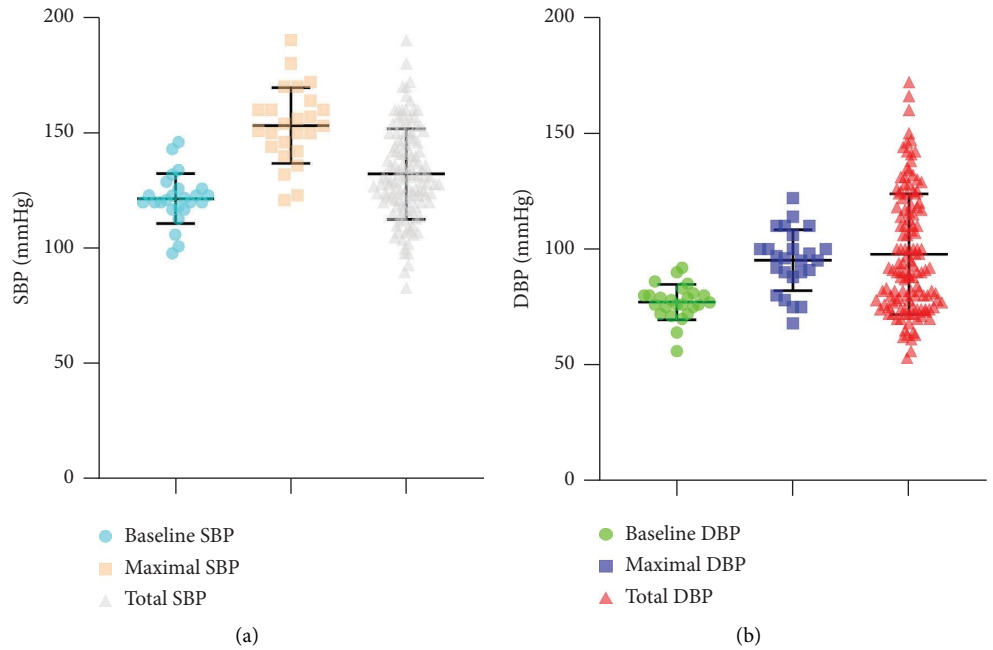

Figure 2: Mean SBP/DBP before and after initiation of apatinib therapy meeting the criteria for apatinib-related HTN ($n = 25$). The scatter plot (a) represents SBP data, and the scatter plot (b) represents DBP data. The middle line within each plot represents the mean. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5: Univariate and multivariable logistic regression analyses of risk factors for apatinib-related hypertension.

Variable	Univariate analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
BMI (kg/m^2)	1.187 (1.003, 1.406)	0.046	1.141 (0.956, 1.361)	0.145
Preexisting HTN	4.929 (1.538, 15.793)	0.007	4.155 (1.252, 13.787)	0.020

OR: odds ratio; BMI: body mass index; HTN: hypertension.

The rate of apatinib-related HTN was observed in 25/55 (45.45%) patients, which was higher than the 35.2–40.4% incidence reported in earlier phase II/III clinical trials [4, 22]. Potentially, there are several reasons for this difference. First, prior apatinib trials had strict inclusion and exclusion criteria, which means that many of the patients with uncontrolled HTN may not have been enrolled. Therefore, these sources of data may underestimate the incidence of hypertension and other cardiovascular toxicities. Second, the definition of HTN has changed. The defnitions of HTN based on CTCAEv3.0 [23] was considered as asymptomatic, transient (<24 hrs) increase by > 20 mm·Hg (diastolic) or to >150/100 if previously within normal limits. This was different from the guidelines established by the CTCAEv5.0 and JNC8 definitions, which specified grade 1 HTN as SBP 120–139 mm·Hg or DBP 80–89 mm·Hg. Last but not least, alertness to treatment-related HTN with anti-VEGF therapy has increased. Therefore, clinicians may be paying closer attention to HTN and carefully monitoring BP during treatment.

In addition to apatinib, hypertension was also reported as a complication of treatment with other small molecule TKIs, such as sorafenib [24], sunitinib [25], lenvatinib [26], and axitinib [27]. Among these TKIs, the absolute risk of

hypertension is substantial. For patients treated with sorafenib, the overall incidence of all-grade and high-grade (i.e., grade 3 or 4) hypertension was 23.4% (95% CI 16.0, 32.9%) and 5.7% (2.5, 12.6%), respectively [24]. For patients receiving sunitinib, the incidence of all-grade and high-grade hypertension was 21.6% (95% CI: 18.7, 24.8%) and 6.8% (95% CI: 5.3, 8.8%), respectively [25]. Therefore, it appears that the incidences of hypertension associated with these TKIs are notably similar.

In our study, the mean increases in SBP and DBP from initiation to apatinib-related HTN were 13.83 mm·Hg and 7.82 mm·Hg, respectively. The median time to onset of apatinib-related HTN was 25 days. Our results were in line with earlier TKI trials that observed BP changes in metastatic renal cell carcinoma (mRCC) patients treated with sunitinib and other anti-VEGF TKIs [28, 29]. In a multicenter prospective study of 84 mRCC patients, Catino et al. observed changes in blood pressure for 3.5 weeks during sunitinib treatment, and they found that the mean SBP increased by 9.5 mm·Hg and the mean DBP by 7.2 mm·Hg [27]. Waliany et al. found mean increases in SBP of 8.5 mm·Hg ($p < 0.001$) and DBP of 6.7 mm·Hg ($p < 0.001$) after VEGF TKI therapy, and the greatest increases were observed with axitinib [29].

The results of our study were consistent with these previous findings, with an association between the development of apatinib-related HTN and preexisting hypertension. Hamnvik et al. reported that preexisting hypertension (OR 1.56; 95% CI 1.27, 1.92) was a risk factor for hypertension in anti-VEGF therapy [30]. Yang et al. found that hypertension medical history was an independent predictive factor for the occurrence of hypertension after antiangiogenic treatment [31, 32]. Moreover, Pinkhas et al. reported that there was an association between the development of pazopanib-induced HTN and the presence of baseline prehypertension [33]. An observational prospective cohort study proved that hypertension was the most frequently reported comorbid ailment (38%) in patients with cancer [34]. This report likely understates the current prevalence of hypertension among cancer patients because it was published before the widespread launch of numerous targeted medicines associated with hypertension. Cancer and hypertension have common risk factors and have overlapping pathophysiological mechanisms, and hypertension may also be a risk factor for some tumors [35]. Several observational studies have suggested that hypertension is an independent risk factor for renal cell carcinoma [36]. In addition to potential pathophysiological links between cancer and hypertension, massive and novel cancer therapies, such as TKIs, have been shown to be associated with HTN.

TKIs have been associated with an increased incidence of HTN, and some of the risk factors include preexisting HTN, diabetes mellitus, established cardiovascular disease and renal disease, organ damage, old age, cigarette smoking, and dyslipidemia [37]. According to a previous study [22], patients given apatinib as a once-daily regimen had fewer grade 3 to 4 AEs and a lower incidence of hypertension than those given apatinib as a twice-daily regimen. Of note, the effect of age on the development of hypertension remains unclear. Hamnvik et al. reported that age above 60 years (OR 1.26; 95% CI 1.06, 1.52) was an independent risk factor [30]. In contrast, Price et al. found that there were no major differences in toxicity patterns between those aged ≥ 75 years and those aged < 75 years [38]. Obermannová et al. compared the incidence of all grades of hypertension and grade 3/4 hypertension within the <65 and ≥65 age groups. They found that hypertension associated with treatment was elevated to a similar extent in both age subgroups [39].

In addition, although the occurrence of hypertension is one of the side effects of VEGF inhibitors, it can also be considered a potential predictor of tumor response [40]. Several potential biomarkers have been reported to predict the response of patients to apatinib. Compared to genetic test markers, adverse events are highly effective and easier to implement in treatment institutions on a large scale [41]. The association between the development of hypertension and survival in GC has also been reported previously. It has been reported that the occurrence of hypertension, proteinuria, and/or hand and foot syndrome are independent factors associated with better survival outcomes [42]. Moreover, the development of hypertension may indicate a favorable prognosis in several cancers, such as breast cancer [43, 44], hepatocellular carcinoma [45], nonsmall cell lung cancer, and sarcoma [46–48]. Nevertheless, the current level of evidence that the occurrence of hypertension is a potential biomarker associated with greater efficacy and prolonged survival is not high, and biomarkers of apatinib response differ according to the form of cancer. Therefore, it is necessary to carry out prospective clinical trials with large sample sizes and perform survival analysis.

There are several limitations of this study. First, the inclusion criteria of this study were not stringent. Second, this was a single-arm observational study without a control group, which is typically limited to patients with a good performance status or without selected comorbidities. Last, the sample size of the patient cohort was relatively small. It is, therefore, considered important to conduct a large study that will facilitate identifying more clinical risk factors in a broader patient population.

5. Conclusion

In conclusion, the information on apatinib-related HTN in this study is thought to be meaningful and offers useful information for treatment considerations and monitoring of GC. The incidence of HTN was high in patients treated with apatinib, and preexisting HTN was an independent risk factor. It is important to provide thorough and close monitoring for patients during treatment with apatinib, especially for those with preexisting HTN.

Data Availability

Data will be available upon reasonable request.

Disclosure

The manuscript was already published as a preprint based on the link https://www.authorea.com/users/586485/articles/624594-evaluation-of-apatinib-related-hypertension-and-identification-of-clinical-risk-factors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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