Evaluation of apatinib-related hypertension and identification of clinical risk factors

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Abstract

Background: Antineoplastic therapy with the tyrosine kinase inhibitor (TKI) apatinib in patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (GC) has been associated with hypertension (HTN), but little is known about predisposing clinical characteristics. This study describes the real-world association between baseline clinical characteristics and blood pressure (BP) response in patients prescribed apatinib with GC. Methods: 55 GC patients treated with apatinib were collected from the 1st December 2016 to the 1st December 2020 using medical records retrospectively. Outcomes were defined using the National Cancer Institute’s Common Terminology Criteria for Adverse Events v5.0. Univariate and multivariable logistic regression were used to investigate potential clinical risk factors. Results: 45.45% of patients were evaluated for apatinib-related HTN and Grade 3 HTN occurred 16.36% of patients. Median maximal systolic blood pressure (SBP) during apatinib treatment was 153 mmHg with median time to event of 25 days. New-onset HTN occurred in 10/33 (30.30%) patients. pre-existing HTN (odds ratio [OR]: 4.155; 95% confidence interval [CI]: 1.252-13.787; p =0.020 was key independent risk factors associated with apatinib-related HTN. Conclusions: More thorough BP monitor prior to starting apatinib especially in patients with pre-existing hypertension may reduce cardiovascular risk.

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Abstract

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hypertension (HTN), but little is known about predisposing clinical characteristics. This study describes the real-world association between baseline clinical characteristics and blood pressure (BP) response in patients prescribed apatinib with GC.

**Methods:** 55 GC patients treated with apatinib were collected from the 1st December 2016 to the 1st December 2020 using medical records retrospectively. Outcomes were defined using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Univariate and multivariable logistic regression were used to investigate potential clinical risk factors.

**Results:** 45.45% of patients were evaluated for apatinib-related HTN and Grade 3 HTN occurred 16.36% of patients. Median maximal systolic blood pressure (SBP) during apatinib treatment was 153 mmHg with median time to event of 25 days. New-onset HTN occurred in 10/33 (30.30%) patients. Pre-existing HTN (odds ratio [OR]: 4.155; 95% confidence interval [CI]: 1.252-13.787; \( p = 0.020 \)) was key independent risk factors associated with apatinib-related HTN.

**Conclusions:** More thorough BP monitor prior to starting apatinib especially in patients with pre-existing hypertension may reduce cardiovascular risk.

**Keywords:** Apatinib, Vegf, Hypertension, Angiogenesis inhibitors, Small molecule tyrosine kinase inhibitors, Risk factors

1. Background

Angiogenesis is a rate-limiting step in many pathologic processes including malignant tumor growth\(^1\). Vascular endothelial growth factor (VEGF), as a major growth factor regulating angiogenesis, plays a critical role in the occurrence and development of tumors\(^2\). The importance of VEGFR-2 signaling as a therapeutic target in advanced or metastatic gastric or gastroesophageal junction adenocarcinoma was confirmed in the phase III trial, which demonstrated a modest but significant survival benefit for the VEGFR-2 inhibitor apatinib after progression on second-line chemotherapy\(^3\). In China, approximately 396,500 patients are diagnosed with gastric cancer each year\(^4\). According to the data from National Cancer Center (NCC) of China, the average age at diagnosis of gastric cancer was 67.35 years\(^5\), many of them were at increased risk or had pre-existing 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 tyrosine kinase inhibitors (TKI), that potently suppressed the kinase activities of VEGFR-2, c-kit and c-src, and inhibited cellular phosphorylation of VEGFR-2, c-kit and PDGFR\(^6\). apatinib was approved for the treatment of adenocarcinoma of the stomach or gastroesophageal junction and hepatocellular carcinoma by the National Medical Products Administration (NMPA) in 2014 and 2020. More importantly, in a series of subsequent clinical studies, apatinib also showed significant survival benefit and good safety in the treatment of other multiple tumor species\(^7\)-\(^9\). However, Hypertension (HTN), the most common adverse effects of anti-angiogenic inhibitors, was usually observed for the VEGF/VEGFR inhibitors. In particular, which can cause secondary hypertension or make existing hypertension worsen\(^10\), \(^11\). The incidence of apatinib-related HTN (any grade) was 46.4%. And the incidence of HTN (grade 3/4) was 24.0%\(^3\). The mechanism of HTN in patients receiving anti-VEGF therapy remains unclear. Decreased NO/PGLI\(_2\) secretion by endothelial cells/platelets, abnormal blood vessel density (small vessels and capillaries), vascular stiffness, endothelin dysfunction may contribute to HTN\(^12\)-\(^14\).

The development of clinically significant 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 have not been well characterized. In addition, the occurrence of treatment-related hypertension is frequent, but clinical risk factors for the development of hypertension are rarely reported. Therefore, we aimed to evaluate the hypertensive toxicity associated with apatinib and identification of clinical risk factors in real-world gastric cancer patient population.

2. 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. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[15]

2.2 Study participants

We retrospectively identified all patients treated with apatinib from the 1st December 2016 to the 1st December 2020 using electronic medical records (EMR). 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 enrolled. Patients were excluded if apatinib therapy was stopped fewer than 28 days after initiation, or if the medical record was not complete or BP data was missing. 177 patients were excluded and the remaining 55 patients formed the final cohort for this study. All 55 patients were followed-up until either death occurred or until their last visit. Follow up was completed in September 2022.

Demographic and baseline data were collected for each patient, including sex, age at apatinib start date, body mass index (BMI), medical histories (HTN, diabetes, congestive heart failure, dyslipidemia and coronary artery disease), concomitant medications (angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARBs), beta-blockers (BBs), calcium-channel blockers (CCBs), diuretics, statins, and metformin at or before study entry date), smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, number of metastatic sites, clinical tumor, node, and metastasis (TNM) classification, operation history, prior radiotherapy, combined therapy, starting apatinib dose, dose adjustment and reason. Validation by manual chart review of patient medication lists and oncologic provider documentation in the EMR was performed for each patient to ensure accuracy of apatinib treatment.

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 SDP following apatinib use were determined based on mean blood pressure measured at each hospital visit, which consisted of at least two visits (one at two weeks after apatinib initiation and one at four weeks after initiation of treatment).

2.4 Definition of pre-existing hypertension

The occurrence of apatinib-related HTN was the primary outcome of the study. Patients were considered to have pre-existing 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) 8[17], SBP[\text{≥}140\text{mmHg} \text{or DBP[\text{≥}90}\text{mmHg} \text{on the average of two or more properly measured, seated, BP readings on each of two or more office visits. In those patients without pre-existing HTN, the occurrence of any of the above criteria during apatinib treatment was defined as apatinib-related HTN.}

2.5 Definition of apatinib-related hypertension

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

2.6 Statistical analysis

Continuous variables are summarized with 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 count and percentages for each level of the variable[18]. 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 using 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, age, BMI, TNM classification, operation history, prior radiotherapy, smoking history, number of metastatic sites(0−2 [?][3], starting apatinib dose, pre-existing HTN and diabetes, baseline SBP and SDP, ECOG PS(0,1,[?][2]), concomitant medications(ACEi/ARBs, CCBs, beta-blockers). ORs with 95% confidence intervals (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(\(p <0.05\)), multivariable logistic regression were conducted to identify independent factors associated with development of apatinib-related HTN.

3. Results

3.1 Patient demographic and baseline characteristics

Between 1st December 2016 to the 31st September 2020, 232 patients received apatinib at our hospital, of which 55 patients were enrolled in the study, 177 patients were excluded because they had only once visit or EMRs had incomplete baseline characteristics or BP measurement.

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 (83.1%) 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, 15 (27.27%) were taking antihypertensive drug treatment. 36.36% had smoking history, 40.00% of the patients received prior operation and 5.45% received prior radiotherapy. The initial dose of apatinib ranged from 125mg once daily to 850mg once daily, the majority of patients were started on the dose of apatinib 125-250mg 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 mmHg vs. 119.53±8.38, \(p =0.413\)) and DBP (77.16±7.59 mmHg vs. 76.63±5.97, \(p =0.770\)).

After Adjusting for baseline blood pressure, relative to baseline SBP, SBP are associated with a significant increase (\(F=15.929, p =0.000\)) in apatinib-related HTN of 14.340 (95% CI:9.157, 19.524) mm Hg and in no apatinib-related of 0.341 (95% CI:-4.388-5.070) mm Hg, respectively. And relative to baseline DBP, DBP are associated with a significant differences(\(F=5.093, p =0.028\)) in apatinib-related HTN of 7.948 (95% CI:3.956-11.941) mm Hg and in no apatinib-related of 1.867 (95% CI:-1.777-5.511) mm Hg, respectively.

3.3 Description of theApatinib-related HTN

In total, 25/55 patients(45.45%)were evaluated for apatinib-related HTN and Grade 3 HTN occurred in 9/55 patients(16.36%). During the follow-up until 28 days following the final dosage of apatinib, no patient experienced grade 4 or grade 5 HTN. Time to new onset of apatinib-related HTN was 25 days (IQR: 13-42 days). Of the 33 patients without pre-existing HTN, 10 (30.30%) developed new-onset HTN, and the median time to onset of HTN was 22.5 days (IQR: 10-54.5 days). Among 22 patients with pre-existing HTN, 15 met criteria for apatinib-related HTN, with a median time to event of 25 days (IQR, 16-40 days) . An antihypertensive drug was started or increased in dose in 15 different episodes in total. The majority of these were CCBs (53.33%) and beta-blockers (26.67%). (Table 4). As shown in Fig. 1, apatinib treatment resulted in a considerable rise in SBP and DBP from baseline to the maximum measurement, with an total
median SBP and DBP after apatinib exposure 9 mmHg and 14 mmHg higher than baseline, that mean SBP and DBP of the patients increased by 7.44% and 18.18%, respectively.

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

4. Discussion

Our study has evaluated the risk factors of HTN in GC patients receiving apatinib by the retrospective study and analyzed all BPs measured at oncology clinics to quantify the changes in hypertension relative to baseline. This study demonstrated a high incidence of hypertension (all-grade: 45.45%; high-grade: 6.8%,) associated with apatinib in GC patients. The majority of apatinib-related HTN were grade I or II, high-grade toxicity can 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 the previous study[19]. In a meta-analysis of 820 patients from 7 prospective trials who were treated with apatinib therapy, the incidences of all-grade and grade 3 or 4 hypertension were 45.4% and 9.7%[20]. In order 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 for overall mortality and cardiovascular-specific fatal and nonfatal outcomes[21]. Therefore, it is important to recognize and manage apatinib-related HTN appropriately.

In our study, the mean increase in SBP and DBP from initiation to apatinib-related HTN was 13.83 mmHg and 7.82 mmHg respectively. And the median time to development of apatinib-related HTN occurs rapidly was 25 days. Our results were in line with those of earlier TKI trials that looked at BP changes in metastatic renal cell carcinoma (mRCC) patients with sunitinib[28] and other anti-VEGF TKIs[29]. Catino et al.[28]detected following 3.5 weeks of sunitinib, mean SBP increased by 9.5 mmHg and DBP by 7.2 mmHg in a multi-center prospective study of 84 mRCC patients. Waliany et al.[29] found a mean increases in SBP of 8.5 mm Hg (\( p <0.0001 \)) and DBP of 6.7 mm Hg (\( p <0.0001 \)) and greatest increases are observed with axitinib.

Our study are consistent with these previous findings, with an association existing between the development of apatinib-related HTN and pre-existing hypertension. Hamnvik et al [30] reported that pre-existing
hypertension (OR 1.56; 95%CI 1.27-1.92) was a risk factor. And Yang et al [31] and Wang et al [32] found that hypertension medical history was an independent predictor factor for occurrence of hypertension after anti-angiogenic treatment. Moreover, Pinkhas et al [33] reported that there were an association existing between the development of pazopanib-induced HTN and presence of a baseline prehypertension. 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, have overlapping pathophysiological mechanisms and hypertension may also be a risk factor for some tumor types [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 associate with HTN.

TKIs have been associated with increased incidence of HTN, some of the risk factors include pre-existing HTN, diabetes mellitus, established CV disease and renal disease, organ damage, old age, cigarette smoking, dyslipidemia, and so on [37]. According to previous research [22], patients given apatinib as a once-daily regimen had fewer grade 3 to 4 AEs than those given apatinib as twice-daily regimen. The incidence of hypertension was also reduced. Of note, the effect of age on the development of hypertension remains unclear, Hamnvik et al [38] reported that age above 60 years (OR 1.26; 95%CI 1.06–1.52) was independent risk factors. On the contrary, Price et al [39] found that there were no major differences in toxicity patterns between aged ≥75 years and <75 years. Obermannova et al [39] compared the incidence of all grade hypertension and grade 3/4 hypertension within the <65 and ≥65 age groups and found that those hypertension associated with treatment were elevated to a similar extent in both age subgroups. The same results held true for subgroups defined by age 75.

In addition, the occurrence of hypertension is thought to be targeted by VEGF inhibitors and it can be considered as a potential predictor of tumor response [40]. According to the report, several potential biomarkers have been reported to predict the response of patients to apatinib. Compared to the genetic test markers, adverse event are highly effective and easier to implement in the treatment institutions on a large scale [41]. The association between the development of hypertension and survival in GC has also been reported previously, it is reported that the occurrence of hypertension, proteinuria and/or HFS were independent factors associated with better survival outcomes [42]. Moreover, the development of hypertension may indicate a favorable prognosis also reported in other cancers, such as breast cancer [43, 44], HCC [45], NSCLC [46] and sarcoma [47, 48]. Finally based on the available evidence for biomarkers of apatinib response, we predict that apatinib-related hypertension might be markers for a favorable clinical outcome. 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 in form of cancers. So it is necessary to carry out prospective clinical trials with large sample sizes and perform more authentic survival analysis.

There are several limitations of this study, including the absence of stringent patient selection criteria, unlike a clinical trial, and the fact that this was a single-arm observational study without a control group, which is typically limited to patients with a good PS or without selected comorbidities. However, this may suggest that the participants in our study were more representative of real-world research. Secondly, the incidence and risk factors of apatinib-related hypertension show some variations across trials in GC and other common tumor types. Moreover, the sample size of the patient cohort was small and may limit our generalizability. It was therefore considered important for conducting a large study to identify more clinical risk factors in a broader patient population more closely reflecting general oncology practice.

5. Conclusion

In conclusion, the information on apatinib-related HTN in this study is thought to be meaningful, it offers useful information for treatment considerations and monitoring with GC. When administering apatinib, healthcare providers should carefully assess patients to determine whether they have hypertension history.
Following the diagnosis of apatinib-related HTN, it is crucial to closely monitor patient’s condition. According to the phase II and III clinical trials, apatinib treatment significantly improved OS and PFS with an acceptable safety profile in patients with GC. Nevertheless, the risk of HTN should still be closely watched.

Conflict of interest
Authors have no conflict of interest.

References

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23. NCI, NIH, DHHS. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). 2006


36. Kim CS, Han KD, Choi HS, Bae EH, Ma SK, Kim SW. Association of Hypertension and Blood Pressure With Kidney Cancer Risk: A Nationwide Population-Based Cohort Study. Hypertension. 2020;75:1439-46.doi:10.1161/hypertensionaha.120.14820


Table 1 Definitions and severity of the apatinib-related HTN

Hypertension

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 medication indicated; recurrent or persistent (>24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated;
Grade 3 Systolic BP >=160 mmHg or diastolic BP >=100 mmHg; 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, hypertensive crisis); urgent intervention indicated;
Grade 5 Death

BP, blood pressure

Table 2 Patient demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Total Cohort (N = 55)</th>
<th>Apatinib-related HTN (N = 25)</th>
<th>No apatinib-related HTN (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>40(72.73)</td>
<td>19(76.00)</td>
<td>21(70.00)</td>
</tr>
<tr>
<td>Age, years</td>
<td>58.40±10.05</td>
<td>59.84±8.76</td>
<td>57.20±11.02</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.69±3.45</td>
<td>23.72±3.36</td>
<td>21.82±3.33</td>
</tr>
<tr>
<td>TNM classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6(10.91)</td>
<td>1(4.00)</td>
<td>5(16.67)</td>
</tr>
<tr>
<td>IV</td>
<td>49(89.09)</td>
<td>24(96.00)</td>
<td>25(83.33)</td>
</tr>
<tr>
<td>Prior operation</td>
<td>22(40.00)</td>
<td>9(36.00)</td>
<td>13(43.33)</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>3(5.45)</td>
<td>0</td>
<td>3(10.00)</td>
</tr>
<tr>
<td>Smoker</td>
<td>20(36.36)</td>
<td>5(20.00)</td>
<td>15(50.00)</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>51(92.73)</td>
<td>23(92.00)</td>
<td>28(93.33)</td>
</tr>
<tr>
<td>3</td>
<td>4(7.27)</td>
<td>2(8.00)</td>
<td>2(6.67)</td>
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<tr>
<td>Combined therapy</td>
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<tr>
<td>Apatinib Therapy</td>
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<td>Apatinib Therapy</td>
<td>Apatinib Therapy</td>
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<tr>
<td>Initial dose 125-250mg QD</td>
<td>34(61.82)</td>
<td>13(52.00)</td>
<td>21(70.00)</td>
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<tr>
<td>Initial dose 425-500mg QD</td>
<td>20(36.36)</td>
<td>11(44.00)</td>
<td>9(30.00)</td>
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<tr>
<td>Initial dose 750-850mg QD</td>
<td>1(1.82)</td>
<td>1(4.00)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>13(23.64)</td>
<td>7(28.00)</td>
<td>6(20.00)</td>
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<tr>
<td>Pre-existing HTN</td>
<td>22(40.00)</td>
<td>14(56.00)</td>
<td>8(26.67)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>120.49±9.51</td>
<td>121.64±10.77</td>
<td>119.53±8.38</td>
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<td>DBP, mm Hg</td>
<td>76.87±6.70</td>
<td>77.16±7.59</td>
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<td>ECOG PS</td>
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<td>0</td>
<td>14(25.45)</td>
<td>7(28.00)</td>
<td>7(23.33)</td>
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<td>1</td>
<td>33(60.00)</td>
<td>13(52.00)</td>
<td>20(66.67)</td>
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<td>2</td>
<td>8(14.55)</td>
<td>5(20.00)</td>
<td>3(10.00)</td>
</tr>
<tr>
<td>ACEIs/ARBs</td>
<td>6(10.91)</td>
<td>5(20.00)</td>
<td>1(3.33)</td>
</tr>
<tr>
<td>CCBs</td>
<td>5(9.09)</td>
<td>2(8.00)</td>
<td>3(10.00)</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>4(7.27)</td>
<td>3(12.00)</td>
<td>1(3.33)</td>
</tr>
</tbody>
</table>
Data presented as a number with percent (%), mean ± standard deviation.

* Demographic parameters are significantly different between study groups (p<0.05).

HTN, hypertension; QD, once daily; ECOG, Eastern Cooperative Oncology Group performance status; BP, blood pressure; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCBs, calcium channel blocker.

Table 3 Description of the systolic/diastolic blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Apatinib-related HTN</th>
<th>No apatinib-related HTN</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SBP change, mm Hg</td>
<td>14.340 (9.157, 19.524)</td>
<td>0.341(-4.388-5.070)</td>
<td>15.929</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean DBP change, mm Hg</td>
<td>7.948(3.956, 11.941)</td>
<td>1.867(-1.777-5.511)</td>
<td>5.093</td>
<td>0.028</td>
</tr>
</tbody>
</table>

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

Table 4 Description of the Apatinib-related HTN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apatinib-related HTN (N = 25)</th>
<th>Apatinib-related HTN (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median [Q1, Q3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in SBP (mm Hg)</td>
<td>9[0.82, 26.13]</td>
<td>-11, 50</td>
</tr>
<tr>
<td>Change in DBP (mm Hg)</td>
<td>5.75[0, 18.07]</td>
<td>-15.5, 29.67</td>
</tr>
<tr>
<td>Maximal SBP (mm Hg)</td>
<td>153[143, 162]</td>
<td>121, 190</td>
</tr>
<tr>
<td>Maximal DBP (mm Hg)</td>
<td>96[89, 103]</td>
<td>68, 122</td>
</tr>
<tr>
<td>Time until apatinib-related HTN (days)</td>
<td>25[13, 42]</td>
<td>2, 77</td>
</tr>
<tr>
<td>No preexisting HTN</td>
<td>6(24.00)</td>
<td></td>
</tr>
<tr>
<td>Class of antihypertensive started or intensified n (%)</td>
<td>8(53.33)</td>
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</tr>
<tr>
<td>Calcium channel blockers</td>
<td>8(53.33)</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>4(26.67)</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>3(20.00)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as a number with percent (%), or median [1st quartile-3rd quartile].

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

Table 5 Univariate and Multivariable Logistical Regression Analysis of Risk Factors for Apatinib-Related Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR(95%CI)</td>
<td>p-value</td>
<td>OR(95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>1.187(1.003-1.406)</td>
<td>0.046</td>
<td>1.141(0.956, 1.361)</td>
<td>0.145</td>
</tr>
<tr>
<td>pre-existing HTN</td>
<td>4.929(1.538-15.793)</td>
<td>0.007</td>
<td>4.155(1.252, 13.787)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

OR, odds ratio; BMI, body mass index; HTN, hypertension.
Fig. 1 Median SBP/DBP before and after initiation of apatinib therapy meeting criteria for apatinib-related HTN (n = 25). The three boxes on the left represent SBP data, the right side represents DBP data. The light blue box and yellow box mean baseline median SBP and DBP which are 121 mmHg and 77 mmHg respectively. These orange box and deep blue box each represent median maximal SBP and median maximal DBP which are 153 mmHg and 96 mmHg. The grey box and green box indicate total median SBP and total median DBP which are 130 mmHg and 91 mmHg. Solid line within each box represents the median. Boxes represent the interquartile range. Bars represent the range.

SBP, systolic blood pressure; DBP, diastolic blood pressure.