Original Article

Outcomes of minority patients with very severe hypertension (>220/>120 mmHg)

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Objectives: Acute severe hypertension is a common problem among inner-city ethnic minority populations. Nevertheless, the effects of currently employed treatment regimens on blood pressure have not been determined in a clinical practice setting. We determined the SBP responses to acute antihypertensive drug protocols and the 2-year natural history of patients presenting with severe hypertension.

Methods: Retrospective cohort investigation in consecutive patients with SBP at least 220 mmHg and/or DBP at least 120 mmHg during 3-month enrollment in 2014 with 2-year follow-up. Primary outcomes were SBP versus time for the first 5 h of emergency treatment and 2-year follow-up including repeat visits, target organ events, and hospitalizations.

Results: One hundred and fifty-six unique patients met criteria with 69% Black; 34% Hispanic; 56% had previous visits for severe hypertension; 31% had preexisting target injury. *Acute management:* Acute antihypertensive regimens resulted in grossly unpredictable and often exaggerated effects on SBP. Treatment acutely reduced SBP to less than 140 mmHg in 30 of 159 patients. Clonidine reduced SBP to less than 140 mmHg in 19/61. *Two-year follow-up:* We observed 389 repeat visits for severe hypertension, 99 new target events, and 76 hospitalizations accounting for 620 hospital days.

Conclusion: Acute treatment of severe hypertension produced unpredictable and potentially dangerous responses in SBP. Two-year follow-up demonstrated extraordinary rates of recurrent visits, target organ events, and hospitalizations. Our findings indicate a need to develop effective management strategies to lower blood pressure safely and to prevent long-term consequences. Our findings may apply to other hospitals caring for ethnic minority populations.

Keywords: antihypertensive drugs, clonidine, hypertensive crisis, hypertensive target organ injury, hypertensive urgency, severe hypertension

Abbreviations: BP, blood pressure; ED, emergency department

INTRODUCTION

Emergency care of patients with acute severe hypertension without acute target organ injury, commonly referred to as hypertensive urgency, presents two major challenges of providing: first, the best immediate care for the blood pressure (BP) elevation; and second, appropriate long-term management to prevent target organ events.

The best immediate treatment of severe hypertension without acute target organ injury remains unknown. Recent consensus guidelines [1–3] and expert reviews [4–8] advise against immediate lowering of BP, but rather advocate cautious reinstitution or intensification of existing antihypertensive treatment and prompt referral [1–8]. In contrast, other experts recommend a wide array of treatment protocols to lower BP acutely [9–17]. Although a benefit of acutely lowering BP in patients without target organ injury has yet to be demonstrated [18], many physicians may be reluctant to allow severely hypertensive patients to remain for even brief intervals without some form of treatment. Accordingly, the practice in many hospitals is frequently acute drug treatment, often with short-acting oral or intravenous (IV) bolus drugs. Nevertheless, there are few data on the BP responses that result from the application of these protocols in clinical practice [17,19–22].

The second major challenge is to provide appropriate long-term management to prevent target organ injury. Although there are excellent outcome data for malignant hypertension [23], the long-term natural history of patients with severe hypertension but without target injury is unknown. A 6-month follow-up of patients from a large private hospital system with BP at least 180/110 mmHg suggested that with appropriate referral and management the rate of major cardiovascular events may be low [24,25]. On the other hand, there may be important disparities among ethnic minority patients with more severe

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hypertension (≥220/≥120 mmHg) who seek emergency department (ED) treatment [26]. The rates of recurrent ED visits, target organ injury, and hospitalizations may be substantially higher in this population.

The objectives of this retrospective cohort investigation are to determine the clinical characteristics of patients with *very* severe hypertension [29] defined as SBP at least 220 mmHg and/or DBP at least 120 mmHg who presented for care over a prespecified 3-month interval in 2014 at our teaching hospital system; determine acute pharmacological regimens and resulting BP responses to treatment in an actual clinical practice setting; establish the 2-year natural history including recurrent ED visits for hypertension, new-onset target events, and hospitalizations.

METHODS

We conducted a retrospective cohort investigation of patients presenting with SBP at least 220 mmHg and/or DBP at least 120 mmHg within the Jackson Memorial Hospital outpatient clinics and ED over a 3-month enrollment period from 1 January 2014 to 31 March 2014.

We prospectively selected our inclusion BP range to approximate the Joint National Committee 5 [27] criteria for *very* severe hypertension. We selected this range, which is considerably higher than the widely accepted at least 180/110 mmHg, for several reasons. First, very few data exist on patients with extremely high range at least 220/at least 120 mmHg. We hypothesized, based upon clinical experience, that there might be a substantial cohort of patients meeting the at least 220/at least 120 mmHg criteria among our ethnic minority patient population. Second, we considered that the higher entry criteria may at least partly ameliorate the effects of regression to the mean and spurious transient BP readings which are both known to be common in the acute ED setting [28–30]. In addition, a previous pilot study suggested 220/120 mmHg to be a BP range at which many clinicians applied some form of intervention [31]. Furthermore, our studies of the pathophysiology in patients with at least 220/120 mmHg suggest that a number of key mechanisms including endothelial and platelet activation may contribute to an accelerated risk for adverse hypertensive events [32–34].

All study procedures were conducted in accordance with the guidelines and requirements of the University of Miami Human Subjects Research Office (IRB). Because of the retrospective nature of the study, the University of Miami IRB waived informed consent. All patient information was de-identified.

Patients presenting with very severe hypertension were enrolled in chronological order beginning 1 January 2014 through 31 March 2014. Electronic medical records were identified by the Jackson Memorial Hospital IT Department based upon International Classification of Diseases (ICD)-9 and ICD-10 codes and BP criteria. The data were directly collected from the electronic medical record by coinvestigators and validated by two independent reviews.

Patients with obvious secondary hypertension or confounding or situational causes of acute hypertension such as acute pain syndrome, trauma, drug overdose, or acute psychiatric emergency were excluded from analysis.

Baseline and demographic characteristics

We recorded baseline demographic information including age, sex, race, ethnicity, and BMI directly from the hospital record. We documented past medical history including diabetes mellitus, smoking, previous ED or clinic visits for severe hypertension, and existing hypertensive target organ injury. We verified evidence of nonadherence to medication or clinic follow-up based upon physician notes specifically and directly implicating nonadherence. We did not have sufficient data to further evaluate potential root causes of nonadherence.

Clinical presentation and emergency evaluation

We documented presenting symptoms, presence or absence of acute target organ injury, and the clinical evaluation for target organ injury including laboratory testing, ECGs, and funduscopic examination.

Blood pressure determination

BP was determined in the ED utilizing either a Dinamap GE Carescape V100 or Dinamap GE Procare 400 (General Medical Devices Inc., Palatine, Illinois, USA). A single determination was recorded with the patient resting in the seated position. BP measurements at least 180/at least 110 mmHg were repeated to confirm significant BP elevation. BP was also repeated and recorded immediately prior to administration of antihypertensive treatment.

Pharmacological regimens and their resulting blood pressure reductions

We recorded the first antihypertensive agent administered, the total number of agents administered, and BP versus time data resulting from acute antihypertensive treatment. We documented the number of patients with a reduction to less than 160, less than 140, less than 120 mmHg, and acute reductions of at least 100 mmHg over the first 5 h of treatment.

Two-year follow-up data and natural history

We recorded the number of patients who attended a clinic visit within 1 month from the index visit and those lost to follow-up immediately following the index visit. We documented repeat ED visits for severe hypertension and new onset hypertensive target organ events over a 2-year period. We determined the number of hospital admissions for severe hypertension and related target events and the number of hospital days generated by these admissions.

Target organ events

We predefined target organ events as new onset episodes of acute coronary syndrome, heart failure, cerebrovascular accident, myocardial infarction, acute kidney injury, incident chronic kidney disease, and fatal cardiac arrest. We recorded target events from existing clinical data based upon the final diagnosis of the physician caring for the patient and in the context of supporting clinical (e.g. medical history, cardiovascular, and neurological examinations), laboratory studies, ECG, and radiographic data. Each event was reviewed by two study team members. Data were cross-checked by the study principal investigator (R.A.P.).

Statistical methods

Demographic characteristics were summarized via simple frequencies and percentages. For construction of the mean (SD) BP versus time curves, we defined the time of the first BP measurement as time zero. To allow summary measure computation at hourly intervals we binned (grouped) the data as follows: measurements that occur up to 60 min after first measurement were coded as hour 1, measurement between 60 (inclusive) and 120 min were coded as hour 2, up to hour 5. For the 20-h BP data hours 0–20, we employed 5-h bins due to the reduced number of BP measurements after hour 5.

For survival data on time to repeat ED visit and time to new target organ event, Kaplan–Meier curves were produced for both the aggregate and subgroup level [35]. Predefined subgroups for the respective survival data included previous ED visit versus no previous ED visit, and previous target organ event versus no previous target organ event. Subgroup differences in survival were assessed via log-rank tests [36]. For BP time course data, individual longitudinal data curves were produced for both aggregate and subgroup data, in which subgroups represented nine drug treatment regimens. Statistical tests were considered statistically significant at alpha 0.05. All analysis was conducted using R statistical software [37].

RESULTS

Of 5996 Medical ED visits from 1 January 2014 through 31 March 2014, 181 hospital encounters met the inclusion BP criteria. Of the 181 encounters, 22 cases were excluded from analysis because of identifiable situational causes of severe hypertension. We included in our analysis 159 visits by 156 patients comprising 2.65% of the 3-month ED census with SBP at least 220 mmHg and/or DBP at least 120 mmHg.

Baseline and demographic characteristics

Baseline and demographic information for the 156 patients are presented in Table 1. One hundred and fifty-one patients (97%) were either Black, Hispanic, or both Black and Hispanic. Thirty-six patients (23%) had diabetes mellitus, 57 (37%) were obese, and 37 (24%) were smokers. Eighty-seven patients (56%) had previous ED visits for treatment of severe hypertension. Eighty-eight patients (56%) had a documented history of nonadherence to prescribed medical treatment and/or follow-up. Forty-eight patients (31%) had existing target organ injury (Table 1).

Clinical presentation and emergency evaluation

Sixty-eight patients were asymptomatic (Table 1). These patients were discovered to have severely elevated BP and referred from internal medicine or medical subspecialty clinics ($N = 22$), correctional facilities ($N = 23$), routine visits for medication refills ($N = 14$), or self-referral for BP check ($N = 9$).

Forty-two patients presented with mild vague somatic complaints not clearly related to elevated BP. Emergency evaluation for potential target organ injury for the 159 visits was generally quite limited and consisted primarily of serum creatinine 116 (73%), ECG 53 (33%), and urinalysis 41 (26%). Only two funduscopic examinations were performed.

TABLE 1. Demographic characteristics and clinical presentation ($N = 156$)

Age (SD)	54.9 (SD 11.6)
Over 50 years	110 (70)
(40–50) years	27 (17)
Under 40 years	19 (12)
Sex	
Men	89 (57)
Women	67 (43)
Race/ethnicity	
Black	108 (69)
African American	65 (42)
Haitian American	30 (19)
Hispanic	10 (6)
African-Caribbean	3 (2)
White	48 (31)
Hispanic	43 (28)
Non-Hispanic	5 (3)
Medical history	
Drugs/alcohol	11 (7)
Smoking	37 (24)
Diabetes mellitus	36 (23)
BMI mean (SD)	29.14 (SD 6.40)
Class I obesity (30.0–34.9)	24 (15)
Class II obesity (35.0–39.9)	23 (15)
Class III obesity (40.0+)	10 (6)
Total obese	57 (37)
Previous visits due to severe hypertension	87 (56)
Evidence of nonadherence to medications	88 (56)
History of target organ injury	48 (31)
Cerebrovascular accident	22
Chronic kidney disease	17
Myocardial infarction	16
Congestive heart failure	11
Coronary artery disease	6
Left ventricular hypertrophy	5
Cardiomegaly	1
Aortic dissection	1
Peripheral vascular disease	1
Medical care funding	
Corrections health services/Mia-Dade	50 (30)
Nonfunded/self-pay	32 (20)
Funded	73 (46)
Private insurance	25 (16)
Medicare	23 (15)
Medicaid	15 (9)
Hospital financial assistance	8 (5)
Entrant impact Grant-Cuba	1 (0.5)
Clinical presentation	
Asymptomatic	68 (43)
Nonspecific somatic complaint	42 (26)
Headache	35 (22)
Epistaxis	4 (3)
Acute target organ injury	14 (9)
Acute kidney injury	8
Heart failure	4
Acute coronary syndrome	4
Clinical evaluation	
Serum creatinine	116 (73)
ECG	53 (33)
Urinalysis	41 (26)
Funduscopic examination	2 (1)

Number (%).

Acute pharmacological regimens and resulting blood pressure reductions

One hundred and forty-seven patients (92%) received acute antihypertensive drug treatment (Table 2) in 159 visits.

TABLE 2. Acute pharmacological management and blood pressure reduction (159 visits)

Number of antihypertensive drugs administered	*N* (%)
1 medication	78 (49)
2 medications	47 (30)
3 medications	13 (8)
4 medications	9 (6)
No medications	12 (8)
First antihypertensive administered	
Oral clonidine	61 (38)
Oral clonidine alone single dose	37 (23)
Oral clonidine alone 2 or more doses	6 (4)
Oral clonidine first drug in multiple drug regimen	18 (11)
ER nifedipine	31 (19)
IV hydralazine	18 (9)
Oral lisinopril	10 (6)
Oral amlodipine	9 (6)
Oral metoprolol	6 (4)
IV labetalol	4 (3)
Oral HCTZ	4 (3)
Oral hydralazine	3 (2)
IV metoprolol	1 (0.6)
Oral labetalol	1 (0.6)
IV furosemide	1 (0.6)
Oral enalapril	1 (0.6)
Reduction of SBP while in the ED	
Acute reduction of SBP by more than 100 mmHg	14
Oral clonidine	11
Oral clonidine alone single dose	5
Oral clonidine alone 2 or more doses	1
Oral clonidine first drug in multiple drug regimen	5
IV hydralazine alone single dose	2
Oral amlodipine first drug in multiple drug regimen	1
Reduction of SBP to below 160 mmHg	77
Oral clonidine	38
Oral clonidine alone single dose	25
Oral clonidine alone 2 or more doses	3
Oral clonidine first drug in multiple drug regimen	10
ER nifedipine	13
ER nifedipine alone single dose	3
ER nifedipine alone 2 or more doses	1
ER nifedipine first drug in multiple drug regimen	9
IV hydralazine	5
IV hydralazine alone single dose	3
IV hydralazine first drug in multiple drug regimen	2
No medications	7
Others[a]	14
Reduction of SBP to below 140 mmHg	30
Oral clonidine	19
Oral clonidine alone single dose	9
Oral clonidine alone 2 or more doses	3
Oral clonidine first drug in multiple regimen	7
IV hydralazine	3
IV hydralazine alone single dose	2
IV hydralazine first drug in multiple regimen	1
ER nifedipine	2
Oral lisinopril	1
No medications	5
Reduction of SBP to below 120 mmHg	9
Oral clonidine	5
Oral clonidine alone single dose	3
Oral clonidine alone 2 or more doses	1
Oral clonidine first drug in multiple drug regimen	1
IV hydralazine alone single dose	2
No medications	2
Increase in blood pressure	18

[a]Five oral lisinopril, three oral amlodipine, two IV labetalol, one oral hydralazine, one oral metoprolol, one oral enalapril, one oral HTCZ. ED, emergency department; ER, extended release; IV, intravenous.

Twelve patients received no treatment. Seventy-eight patients received a single antihypertensive drug. Patients received multiple drug regimens based upon BP determinations conducted at widely varying time intervals. Clonidine was administered as the first agent in 61 patients, including $N=37$ as a single dose, $N=6$ as repeated doses, and $N=18$ as the first drug in combination with other agents. Eighteen patients received IV hydralazine and 31 patients ER nifedipine.

Figure 1a displays the mean (SD) SBP versus time for the first 5 h of treatment. The mean (SD) plot suggests a rather smooth and gradual reduction in SBP over the first 5 h of treatment. Nevertheless, the mean (SD) plot in Fig. 1a masks the wide range of SBP responses to treatment and does not adequately reflect the SBP responses across individual patients. Figure 1b displays box plots of SBP versus time and Fig. 1c box plots of the change in SBP for the first 5 h of treatment for the entire cohort. Figure 1b and c reveal the extremely wide *ranges* of the responses to acute antihypertensive treatment. Figure 1b and c demonstrate that acute treatment with oral and IV antihypertensive drugs resulted in grossly unpredictable and often exaggerated effects on SBP. Perhaps even more striking are the plots of individual BP versus time displayed in Supplemental Figs. 1–5, http://links.lww.com/HJH/A995. These individual plots further illustrate the striking unpredictability and potentially dangerous BP reductions associated with acute pharmacologic treatment of very severe hypertension.

Table 2 demonstrates that SBP was acutely reduced to less than 140 mmHg in 30 patients (19%) and to less than 120 mmHg in nine patients (6%), exposing patients to the risk of adverse ischemic events. Fourteen patients (9%) experienced an acute reduction in SBP of more than 100 mmHg. Fortunately, none of these patients experienced an adverse ischemic event related to the extreme reduction in SBP. Of interest, SBP *increased* in 18 patients, further exemplifying the unpredictability of SBP responses to acute drug treatment.

Figure 1d provides a box plot of the median SBP response and *range* of several of the more commonly used drugs clonidine, hydralazine and the extended release long-acting ER nifedipine. The box plot of change in SBP during the first 5 h of treatment demonstrates the wide range of SBP responses to acute management with short-acting oral or IV bolus drugs. For example, the SBP response to a single dose of clonidine ranged from a decrease of 120 mmHg to an *increase* of 38 mmHg. The plots of individual BP and change in BP for nine commonly employed regimens are displayed in Supplemental Figs. 3 and 4, http://links.lww.com/HJH/A995.

Overall, clonidine as the first agent was associated with 19 of 61 patients (31%) having SBP reduced to below 140 mmHg and five below 120 mmHg (Table 2). Clonidine given alone as a single dose ($N=37$) resulted in nine patients (24%) experiencing an acute reduction to less than 140 mmHg and three to less than 120 mmHg (Table 2). Sixteen patients had a drop in SBP of greater than or equal to 80 mmHg and four patients greater than or equal to 100 mmHg.

Two of 18 patients who received IV hydralazine had precipitous reductions in SBP to less than 100 mmHg within

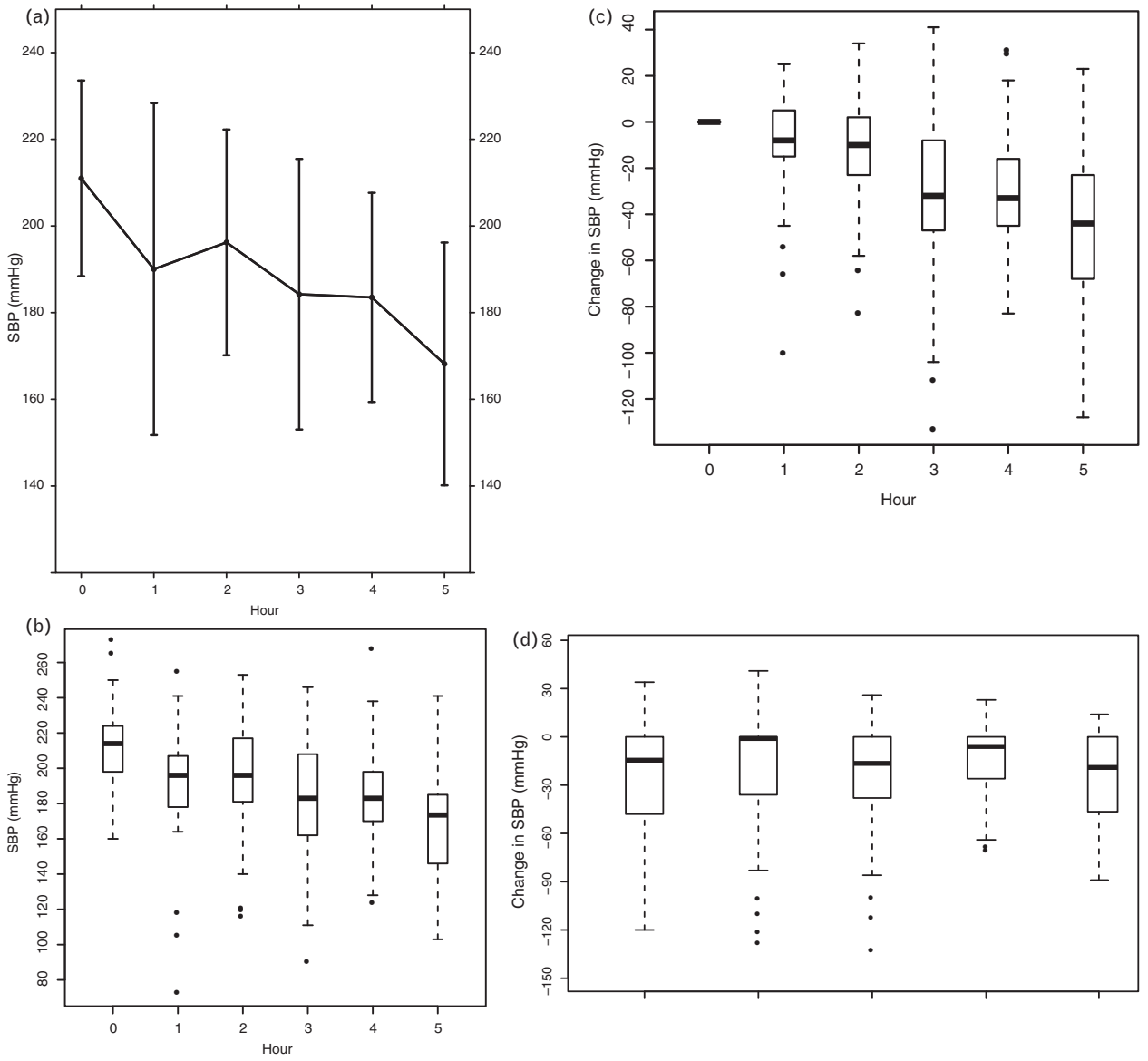

FIGURE 1 SBP versus time and change in SBP from initial value versus time. (a) Mean (SD) SBP versus time for the first 5 h. (b) Box plot of SBP versus time for 159 patient visits. (c) Box plot of change in SBP from initial value versus time for 159 patient visits. 1D box plot of SBP response to several antihypertensive agents.

2 h. Of only four patients treated with IV labetalol, one experienced a drop of more than 100 mmHg. The group that received no drug ($N = 12$) demonstrated seven patients who fell below 140 mmHg and two below 120 mmHg. On the other hand, long-acting drugs had relatively milder responses in SBP but significant reductions to less than 140 mmHg were observed. Long-acting drugs such as ER nifedipine and lisinopril appeared to produce more gradual reduction in BP although the numbers of patients are small and do not allow assertions to be made regarding their superiority over short acting oral and IV bolus drugs.

We collected SBP versus time data out to 20 h. Similar to the values from 0 to 5 h, we noted a wide range of SBP variability. Mean (SD) and box plots of SBP versus time curves out to 20 h are displayed in Fig. 2a and b.

Two-year follow-up: recurrent emergency department visits and new target organ events

Fifty-three patients were immediately lost to follow-up and did not have any clinic or ED visits recorded over the 2-year follow-up period. Of these, 20 were patients cared for by the Corrections Health Services within the Miami-Dade correctional system (Table 1). Only 12 patients attended a scheduled follow-up clinic visit within 1 month. The patients for whom follow-up data were available demonstrated an alarming rate of repeat visits for severe hypertension, new target organ events, and hospitalizations.

Table 3 indicates that 78 patients had at least one repeat ED visit for medical management of severe hypertension. Figure 3a presents the Kaplan–Meier survival curve for the time to a second ED visit and Fig. 3b compares the rate of a

second ED visit in patients with versus without a previous ED visit. This analysis suggests that having a prior ED visit is a significant predictor of a second ED visit. The cohort accounted for 389 new ED visits for severe hypertension over the 2-year follow-up period and 532 ED visits in total.

The hypertensive cohort accounted for 99 new hypertensive target organ events including four deaths in the 2-year

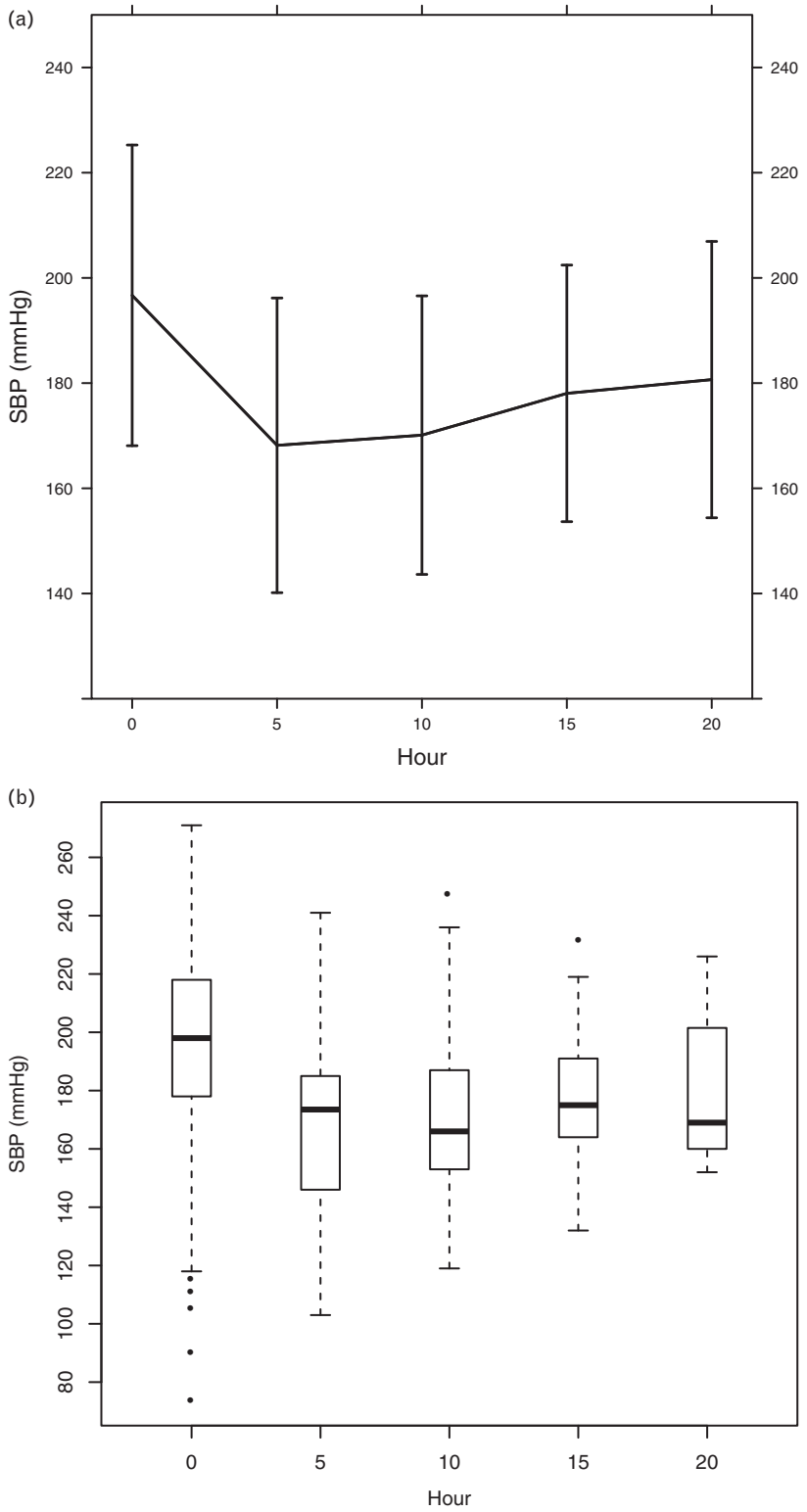

FIGURE 2 Extended plot of SBP versus time for hours 0–20. (a) Extended plot of mean (SD) SBP versus time for hours 0–20. (b) Extended plot of individual SBP versus time for hours 0–20.

TABLE 3. Two-year follow-up: recurrent emergency department visits and new target organ events

Immediately lost to follow-up	53 (34)
Patients with follow-up data	103 (66)
Total clinic visits	365
Attended clinic visit within 1 month of ED discharge	12
Patients with at least one clinic visit	66
Patients with one or more ED visit in 2-year follow-up	78
Total ED visits in 2-year follow-up period	389
Total ED visits over 2 years including index visit	532
Patients with new target organ events	36
Acute target organ events	99
Acute coronary syndrome	29
Heart failure	29
Cerebrovascular accident	12
Acute kidney injury	7
Chronic kidney disease	5
End stage renal disease	4
Newly diagnosed left ventricular hypertrophy	4
Myocardial infarction	4
Aortic dissection	1
Fatal cardiac arrest	4
Patients requiring hospitalizations	29
Number of hospitalizations	76
Total hospital days	620
Average length of stay	8
Average hospital days per patient	21

ED, emergency department.

follow-up interval (Table 3). Figure 3c demonstrates the time to a new target event and Fig. 3d compares the time to a new target event in those with versus those without preexisting target injury. This analysis suggests that having a prior target injury is a significant predictor of a second target injury. There were 76 hypertension-related hospitalizations over the 2-year follow-up period. The hospitalizations required a total of 620 hospital days and averaged eight hospital days per admission.

DISCUSSION

We identified an extraordinarily high-risk cohort of 156 primarily Black and Hispanic patients who presented for emergency treatment over a 3-month period with very severe hypertension characterized by SBP at least 220 mmHg and/or DBP at least 120 mmHg. We consider 156 patients to be a large number given: the brief 3-month enrollment interval, our extraordinarily high BP entry criteria compared with the commonly utilized 180/110 mmHg, the fact that this cohort originates entirely from a single hospital population, and the alarming frequency of target events and costly hospitalizations.

We determined the SBP versus time course for several widely used acute drug protocols in an actual clinical practice setting. Although many experts utilize short-acting oral drugs and IV bolus drugs, we found the SBP responses to acute administration of short-acting oral and IV bolus antihypertensive patients to be extremely unpredictable and potentially dangerous in many cases. Thirty patients (19%) had SBP reduced to less than 140 mmHg within the first 5 h. Nine patients (6%) had the SBP reduced to less than 120 mmHg. Fourteen patients (9%) experienced an acute reduction in SBP of greater than 100 mmHg. Particularly prone to produce such rapid reductions in SBP were oral clonidine and IV hydralazine [21,22]. Our data suggest that there is a high probability of rapid reduction of BP with the associated risk of adverse ischemic events following several commonly employed protocols. It is important to consider this risk in the context that there is no solid evidence that acute lowering of BP over a brief interval is of benefit in the absence of target organ injury [18].

We consider it remarkable for so many patients to demonstrate SBP dropping below 140 and 120 mmHg within the first 5 h of treatment. Current recommendations for most hypertensive *emergencies* in which there is the compelling presence of acute target organ injury, are for an initial reduction of BP by 20–25% acutely, then cautiously to 160/100–110 mmHg over a period of 2–6 h. BP can then be carefully reduced to the normal range over the ensuing 24–48 h [1,38]. The 20–25% guideline derives from earlier investigations in severely hypertensive humans that demonstrate that the autoregulatory limit of central nervous system (CNS) blood flow begins at approximately 20–25% below baseline BP in severely hypertensive patients. Lowering the BP in excess of 20–25% below baseline resulted in significant reduction in CNS perfusion [39,40]. It may be inferred from these experiments that those patients manifesting an acute SBP reduction within 5 h to below 140 or 120 mmHg could be unnecessarily exposed to the risk of adverse ischemic events.

Most published studies evaluating antihypertensive patients in severe hypertension present BP data as curves of mean (SD) BP over time following the institution of an antihypertensive drug. Such mean (SD) curves tend to mask the wide variability in BP response in severely hypertensive patients. We discovered the box plot formulation and individual plots of BP versus time, which demonstrates the unpredictable and erratic responses to treatment, to be much more informative than the mean (SD) curves. The box plots and individual plots reveal the astonishing wide spectrum of BP response to acute drug treatment, including many cases of rapid reductions that are potentially hazardous. This was especially the case with oral clonidine and IV hydralazine.

Although widely utilized for acute severe hypertension, short-acting oral agents such as clonidine and IV drugs such as hydralazine [21,22] lack the control of drug titration and expose patients to a significant risk of overshoot hypotension. Should a dangerous fall in BP occur, these agents cannot be easily reversed. Further, repeated doses of antihypertensive agents with loading protocols can lead to cumulative effects producing delayed hypotension.

On the other hand, carefully conducted studies have consistently demonstrated that simple measures such as quiet rest can produce significant BP reduction in many severely hypertensive patients [17,22,41,42]. Grassi *et al.* [17] demonstrated that 175 of 549 ED patients with BP but without acute target injury had a spontaneous decrease in their BP with 30 min of quiet rest, as defined by a BP of less than 180/110 mmHg and at least a 20 mmHg decrease in SBP or 10 mmHg decrease in DBP. Nielsen [41] demonstrated a substantial reduction of mean SBP and DBP over a 2-h interval of quiet rest. Park *et al.* [42] recently conducted

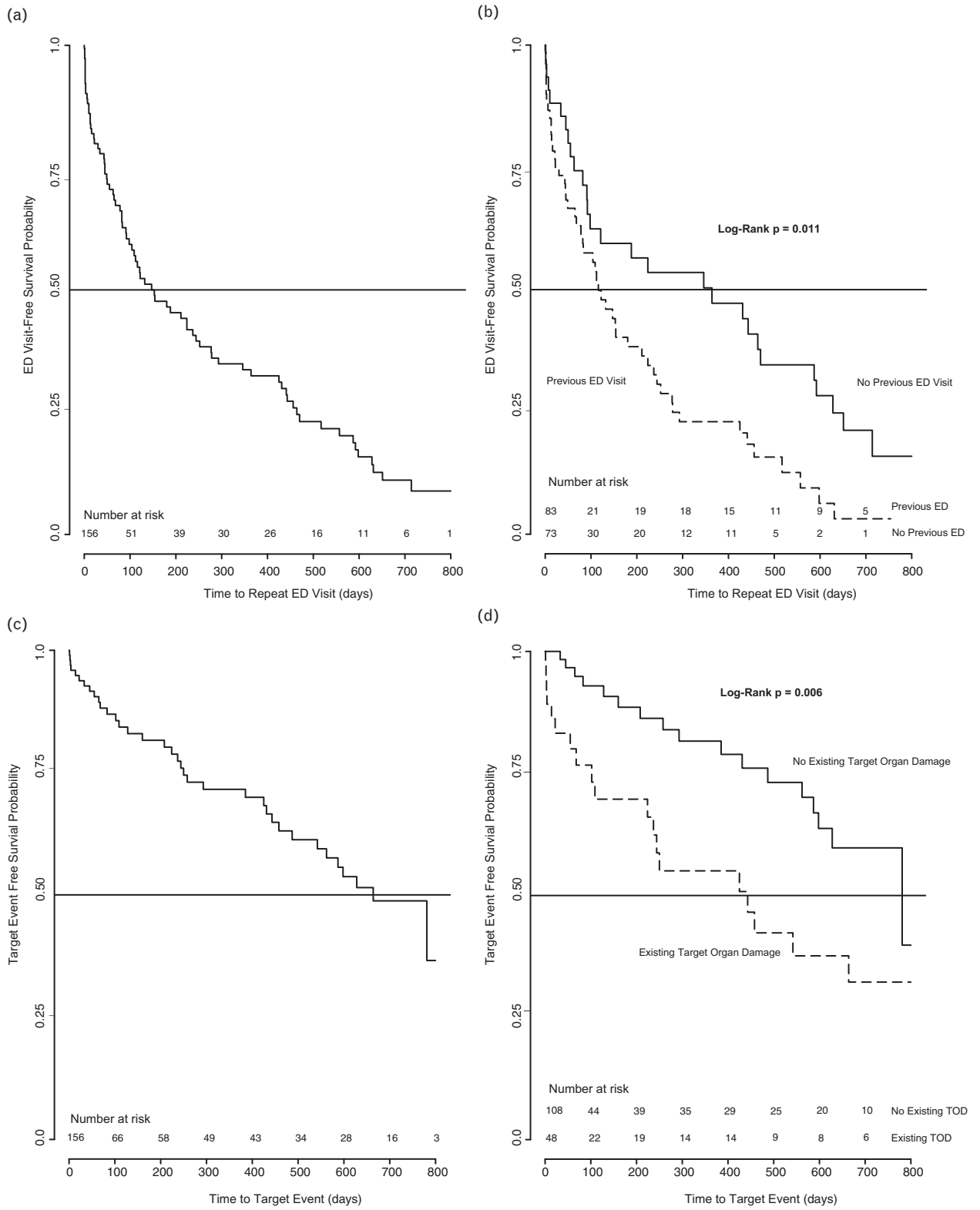

FIGURE 3 Kaplan–Meier survival curves for time to repeat emergency department visit and time to new target organ event. (a) Time to repeat emergency department visit for entire group. (b) Time to repeat emergency department visit for patients with and without history of previous emergency department visit. (c) Time to new target organ event. (d) Time to new target organ event for patients with and without history of previous target organ event. ED, emergency department.

a randomized trial of rest versus antihypertensive treatment and found no difference in BP outcomes.

Our data tend to support the recommendations of several recent consensus documents [1–3], expert reviews [4–8], and clinical research studies [24,25,42] that do not support acute antihypertensive treatment with short-acting oral and IV bolus drugs. These documents instead recommend cautious reinstitution or intensification of existing

treatment and prompt referral. Although our small number of patients do not allow strong assertions regarding antihypertensive efficacy, the BP effects of long-acting drugs seemed to be more gradual and did not produce the drastic drops seen with short-acting oral and IV bolus drugs. This will require further investigation.

The best specific algorithm for management of the patient with very severe hypertension has not been established. Despite many reviews and consensus papers, data to guide the clinician are few. Treatment with short-acting oral and IV bolus drugs may result in unpredictable and potential dangerous drops in BP. In the absence of solid data, one conservative approach to the severely hypertensive patient might be to institute quiet rest for a period of 1–2 h without immediately employing short-acting oral or IV bolus drugs. Determination of which drugs and doses the patient is taking and an evaluation for acute target organ injury could be conducted. At some point during or following this interval, a portion of the existing outpatient antihypertensive regimen may be instituted depending upon the immediate BP response to rest and the clinical circumstances.

We deem it appropriate for the clinician to tailor the clinical evaluation for acute target organ injury to the individual patient and the immediate clinical circumstances. This is especially true in a busy ED setting in which triage decision-making is necessarily rapid. Nevertheless, key components of an evaluation for target organ injury such as funduscopic examination, ECG, urinalysis, and chemistry profile were often absent. Although the funduscopic examination is becoming a less-utilized constituent of the physical examination, it can provide key information in severely hypertensive patients. Given the extreme BP elevation, it is possible that some patients could have had funduscopic evidence of malignant hypertension.

Our study provides striking 2-year follow-up data on recurrent ED visits, specific target events, and hospitalizations. We observed 389 repeat visits for severe hypertension, 99 new onset target events, and 76 hospitalizations accounting for 620 hospital days. Our results contrast with the results from a private sector hospital system. Patel *et al.* reported 6-month follow-up results in patients from a large private hospital system who presented with SBP equal to or greater than 180 mmHg and/or DBP 110 mmHg or more [24,25]. Short-term results suggested that with appropriate referral and follow-up the rate of major cardiovascular events may be very low. Katz *et al.* [43] reported a 90-day hospital readmission rate of 9.3% due to recurrent hypertension in a patient cohort derived from a consortium of 25 academic centers. Levy *et al.* [15] reported a 30-day ED revisit rate of 15.2–18.9%, 30-day all-cause mortality of 0.2%, and a 1-year all-cause mortality of 1.6–2.1%. On the other hand, these well conducted studies did not report long-term data or detailed accounts of recurrent ED visits, specific target organ events, or hospitalizations.

Our single-center cohort had significant preexisting hypertensive target organ injury, history of previous emergency visits for severe hypertension, and tended to be poorly adherent to medical treatment. Many repeat visits and target events were directly related to nonadherence to prescribed medical therapy and follow-up. It was not possible to ascertain the underlying root cause(s) of nonadherence from the existing electronic medical record. Nevertheless, our results suggest that a BP of at least 220/at least 120 mmHg defines an enormous risk for repeat visits, new target organ events, and hospitalizations in our patient population.

Limitations of our study are its retrospective design and the associated tendency for such studies to suffer from missing data and bias. This is particularly the case in adjudicating target events. Our population was comprised primarily of ethnic minorities reflecting the demographic composition of our community. Accordingly our conclusions might not apply to other patient populations. We acknowledge that our findings may possibly be center-specific, but we consider that our results may be representative of other hospitals that care for inner-city populations. Fifty-three patients were lost to follow-up immediately with 20 being from correctional institutions. Therefore, a percentage of the remaining 33 patients could have sought healthcare at other local institutions. Although nonadherence with medical treatment was a key element in many recurrent repeat visits and target organ events, the root cause(s) could not be adequately explored with the existing dataset. We recognize that adherence to medical treatment and follow-up is multifactorial and complex. Clearly, further investigation is indicated.

We consider that our investigation provides several pieces of clinically relevant information. Patients with uncomplicated severe hypertension may present with no symptoms but may also present with vague somatic complaints not specifically related to hypertension per se. Acute treatment with a range of drugs, particularly clonidine and IV hydralazine [21,22], may lead to unpredictable and exaggerated BP responses exposing patients to potential ischemic events. We found that when quantitatively characterizing BP responses to treatment in severe hypertension, individual SBP versus time curves were more informative than summary statistics expressed as mean (SD) which tend to mask striking variability and unpredictability in BP response. The individual data plots identified the large number of patients who experienced exaggerated reductions in SBP.

Our study suggests that very severe uncontrolled hypertension at least 220/at least 120 mmHg confers an immense risk and remains a common but under recognized problem among inner city populations. Patients frequently manifest an exaggerated and potentially dangerous response to commonly utilized short-acting oral and IV bolus drugs. Our 2-year follow-up demonstrated extraordinary rates of potentially preventable recurrent ED visits, target organ injury, hospitalizations and utilization of costly healthcare resources. Although there may be challenges in successfully treating severely hypertensive patients to recommended targets, landmark trials have demonstrated that careful management and drug selection together with close follow-up can achieve and sustain goal BPs to prevent disabling target organ events [44–46].

Our investigation indicates that the BP range at least 220/at least 120 mmHg identifies an important subset of hypertensive patients at extremely high risk for exaggerated BP response to rapid-acting antihypertensive patients, recurrent ED visits, acute target organ injury and costly

hospitalizations. Our results indicate a need to consolidate current management guidelines [1–17], and to develop and test practical algorithms for acute medical management of severe uncontrolled hypertension and to implement effective long-term treatment strategies. We must reiterate the key contribution of nonadherence with prescribed medical treatment and clinic follow-up. Clearly, the central priorities for the management of this patient population will include appropriate follow-up, education, and support to attain optimal adherence to prescribed therapy.

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Conflicts of interest

The authors have no relevant conflicts of interest to report.

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