Original article

**Predictors of 5-year outcomes in malignant phase hypertension:**

**the West Birmingham Malignant Hypertension Registry**

**Short title:** Malignant hypertension and outcomes

Alena SHANTSILA, PhD

Eduard SHANTSILA, MD, PhD

D Gareth BEEVERS, MD

Gregory Y.H. LIP, MD

Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom

# Corresponding author:

# Professor Gregory YH Lip, University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK. Tel: +44 121 507 5080; Fax +121 507 5774; g.y.h.lip@bham.ac.uk

**Conflicts of interest and sources of funding:** None to declare in relation to this manuscript

Word count: 3098

Number of tables: 3

Number of figures: 2

**Abstract**

**Objective:** Malignant hypertension represents a high-risk condition and there are scarce data on current clinical patterns of this condition. The aim of the study is to identify the clinical and demographic factors associated with poor outcome.

**Methods:** The data collected from 1958 till May 2016 included a total of 351 patients whose 5-year survival status was known: 221 white Caucasian (63%, age 51±13 years, 64% male), 83 African-Caribbeans (24%, 45±11 years, 61% male) and 47 South Asians (13%, 42±11 years, 74% male).

**Results**: During the 5-year follow-up 119 (34%) patients suffered a primary outcome, defined as the composite endpoint of death or dialysis. The 5-year mortality ranged from 76% in patients diagnosed before 1967 to 7% in patients diagnosed between 1997-2006. The independent predictors of outcome were advanced age (vs. a reference group of <40 years old; p=0.01 for age at presentation 51-60 years, p <0.001 for age >60 years), prior use of antihypertensive medications (p=0.002), higher serum creatinine (p=0.006), and proteinuria (p<0.01). Also, white Caucasian (odds ratio (OR) 12.02, 95% confidence interval (CI) 1.64– 88.15, p=0.01) and African-Caribbean (OR 15.55, 95%CI 2.06–117.29, p=0.008) origins were associated with higher mortality vs. South Asians. The years of the diagnosis after 1977 were significantly associated with lower composite endpoint of death or dialysis, all p<0.01. **Conclusions**: There has been a major improvement in 5-year survival in patients with malignant hypertension over recent decades. Abnormal renal function at presentation still predicts worse outcome. South Asian ethnicity is also associated with better outcome, although mechanisms involved are yet to be established.

**Key words:** malignant hypertension, dialysis, survival, outcomes

**Condensed abstract:** There has been a major improvement in 5-year survival in patients with malignant hypertension over recent decades. Abnormal renal function at presentation still predicts worse outcome. South Asian ethnicity is also associated with better outcome, although mechanisms involved are yet to be established.

**Introduction**

Malignant hypertension is the most severe form of hypertension, and the diagnosis is based on the presence of extreme elevation in systolic and out of range diastolic blood pressure (usually above 130 mmHg) and Grade III or Grade IV (i.e., with papilledema) retinopathy, according to the classification of Keith, Wagener and Barke[1,2]. Malignant hypertension has been historically linked to poor prognosis and remains a clinical challenge.

The incidence of the malignant hypertension of 1-2 new cases per 100,000 of population per year did not change substantially over five decades of the observation of malignant hypertension series in Birmingham, United Kingdom[3,4]. A similar incidence has been reported in three large malignant hypertension cohorts from Europe[5-7]. The incidence of malignant hypertension in African-Caribbean subjects was generally higher than in White Caucasians with an overall incidence of 7.3 per 100,000 of population per year[5]. Ethnicity is important, as in older published series, black males with malignant hypertension had a worse prognosis, possibly reflecting more severe renal impairment and more severe hypertension at presentation and follow-up[8,9].

Historically if malignant hypertension was left untreated, majority of patients died within two years[1,10]. Following the development of more efficient and tolerable antihypertensive drug therapy, as well as improved awareness and early initiation of treatment, the prognosis has significantly improved[11]. However the prognosis is worse than in non-malignant hypertensive patients, with higher all-cause mortality and prevalence of renal impairment, but better cardiovascular risk profile, then in non-malignant hypertensive patients [12]. Malignant hypertension still represents a high-risk clinical entity and there is scarce data on current epidemiology and clinical pattern of malignant hypertension. The aim of the study is to identify the clinical and demographic factors associated with survival states.

**Methods**

The West Birmingham Malignant Hypertension Registry includes 460 patients diagnosed with malignant hypertension, starting from 1958. The Registry was established by D.G.B. in 1977. It is based on a specialist hypertension clinic City Hospital in Birmingham, UK with multi-ethnic catchment area of West Birmingham. After 1977 all data on new referrals and follow-up were collected prospectively, either from the hospital register, hospital admission or primary care referrals.The catchment area and patient identification mechanisms have been consistent throughout the duration of the registry.The Registry has been described in more detail previously [3]. The clinical diagnosis of the malignant hypertension was based on the presence of severe hypertension and retinopathy with linear flame-shaped haemorrhages, and/or exudates, and/or cotton wool spots with or without papilledema.[13] For the purpose of the current analysis, we have excluded patients with proven glomerulonephritis, polycystic kidney disease, renal cell carcinoma, polyarteritis nodosa, systemic lupus erythematosus or progressive systemic sclerosis (n=26) at the time of diagnosis (Figure 1). These comorbidities alone could lead to the progression to end-stage renal failure or death. The 5-year vital status on May 2016 was known for 351 eligible patients. The primary outcome of the analysis was a combination of death or dialysis. Proteinuria was defined as absent (nil or trace <30mg/dl), mild (30-99mg/dl) or moderate-to-severe (≥100mg/dl)). Left ventricular hypertrophy was identified based on Sokolow-Lyon electrocardiogram voltage criteria, on R wave in V6≥35mm or if the sum of S wave in V1 and R wave in V5 or V6≥35mm. Haematuria was defined as absent or present.

*Statistical analysis*

Statistical analysis was performed by STATA 13 (STATA Inc., USA) software. Data were tested for normality by Kolmogorov-Smirnov test. Continuous variables are presented as mean±standard deviation (SD) and compared by ANOVA for normal data or as median [interquartile range] and compared by Kruskal-Wallis test for non-normal data. Categorical variables are presented as frequency (% of study group) and the actual number compared using χ2-tests. Multivariable logistic regression analysis was used to estimate predictors of the primary outcome in the study population, using the relevant baseline demographic and clinical characteristics. Two-tailed p-value <0.05 was considered as statistically significant.**Results**

A total of 351 patients who had at least 5-year history of malignant hypertension and whose 5-year survival status on May 2016 was known were included in the analysis: 221 White Caucasians (63%, age at presentation 51±13 years, 64% male), 83 African-Caribbeans (24%, 45±11 years, 61% male) and 47 South Asians (13%, 42±11 years, 74% male) (Table 1).

There were significant ethnic differences in demographic and clinical characteristics of patients presenting with malignant hypertension. White Caucasian patients were older than patients from other ethnic groups (p<0.001) and they more often had advanced eye changes with papilledema (p=0.001). South Asian patients included fewer smokers (p<0.001). Patients of African-Caribbean origin had higher diastolic blood pressure and the highest serum creatinine levels at presentation (p=0.04 and p<0.001, respectively). There were no ethnic differences in gender (the majority of patients were male in all ethnic groups), systolic blood pressure, rates of proteinuria and haematuria (p>0.05 for all). South Asian people had significantly lower mortality compared to the other ethnic groups (p=0.015). There were no significant changes in the proportion of patients that were on treatment at the time of the diagnosis over the decades (Table 2). The levels of blood pressure at the time of the diagnosis were similar throughout the decades.

From 119 patients who reached the endpoint at the 5-year follow up, 2 were on dialysis. (Table 1). The main causes of death were chronic renal failure (49.5%), cerebrovascular accidents (20%) and cardiovascular disorders (15%), including 7 deaths due to the acute myocardial infraction. In 13% patients the cause of death was unknown and in 2.5% had other causes of death, with 2 deaths due to the cancer. In the whole cohort of 351 patients non-fatal cardiovascular events occur in 2 patients and non-fatal cerebrovascular events occur in 5 patients, during the 5-year follow up. There was an improvement in 5-year mortality over time, from 76% before 1967 to 7% in patients diagnosed between 1997-2006 (Figure 2).

On multivariable logistic regression independent predictors of the outcome were advanced age (p=0.01 for age at presentation 51 to 60 years, p <0.001 for age >60 years), prior use of antihypertensive medications (p=0.002), higher serum creatinine (p=0.006), proteinuria (p<0.01) (Table 3). Also White Caucasian (odds ratio 12.02, 95% confidence interval 1.64 – 88.15, p=0.01) and African-Caribbean (odds ratio 15.55, 95% confidence interval 2.06 – 117.29, p=0.008) ethnic origins were associated with higher mortality vs. South Asians. The strongest predictor of the outcome was the historical time period of the initial diagnosis, with progressive improvement in the outcome after 1977 (Table 3).

**Discussion**

The study shows continuous improvement in 5-year survival in patients with malignant hypertension over recent decades. This phenomenon was seen stating from 1977 and later, which likely reflects the emergence of new and more efficient antihypertensive agents, as well as improved awareness and early treatment of hypertension[4,8]. Also, over the decades there has been a significant improvement in socio-economic status in the UK overall, and this was also accompanied by the improvement in healthcare service. This may have indirectly improved prognostication in patients with malignant hypertension.

However, certain patient characteristics at presentation with malignant hypertension continue to put them at a high risk of death or dialysis throughout all analysed periods. These characteristics reflect presence of renal dysfunction reflected by high serum creatinine levels and the presence of proteinuria. The observation is consistent with our previous analyses conducted in last 20-years showing that renal impairment independently predicts the survival time, and thus this association remain unchallenged despite newer treatments[4,8,14]. Indeed, malignant hypertension is characterised by histological fibrinoid necrosis of the intrarenal arterioles[15-18]. Also the renin-angiotensin-aldosterone system is activated in patients with malignant hypertension, and this predisposes to abnormalities in electrolyte control by the kidneys, including an increase in tubular sodium reabsorption and water retention[19,20].

Previous studies have shown that presence of malignant hypertension rather than just severe hypertension was associated with an abnormal increase in plasma renin activity and aldosterone release, despite comparable blood pressure[21,22]. Juxtaglomerular ischaemia due to redistribution of blood flow from the kidneys and/or vasculitis of the renal vasculature are likely contributing factors[22]. These data point towards a specific role of the kidneys in the pathogenesis of malignant hypertension. The kidney dysfunction often progressively deteriorates after presentation with malignant hypertension despite the modern treatment and these patients are still at risk of developing of end-stage renal failure[14,23,24]. Adequate long-term blood pressure therefore remains essential for the preservation of kidney function[24,25].

The lack of the predictive value of the left ventricular hypertrophy on the outcome could be explained by regression of left ventricular hypertrophy on echo- and electrocardiogram after normalisation of blood pressure. Partial regression of the hypertrophy can already be seen as early as 2 months after achievement of target blood pressure[26]. Longer treatment results in further, although typically not complete, regression of the left ventricular hypertrophy. Similar trend was also seen in treated malignant hypertension patients from our registry[27]. The proportion of patients on prior antihypertensive therapy was not different between different decades of diagnosis of malignant hypertension. However, the analysis shows that the prior antihypertensive therapy independently predict a worse 5-year outcome.The finding likely indicates that malignant hypertension occurring in patients with pre-existing hypertension bears worse prognosis, although the mechanisms involved are unclear.

Our analyses demonstrate a clear ethnic difference in clinical outcomes with South Asian ethnicity being associated with much better prognosis. Most of the study patients were male, in all ethnic groups. This observation is consistent through the other malignant hypertension series from Europe [5-7]. However the US data from the Nationwide Inpatient Sample database of national discharges from 2000 till 2011 indicate females predominance among patients with malignant hypertension [28]. The reasons for these regional gender differences have not been explored and the role of gender in pathogenesis of malignant hypertension merits further investigation.

The poor prognosis of malignant hypertension was previously linked to black male patients, whilst our contemporary analysis shows that both White Caucasian or African-Caribbean of either gender are now at higher risk of unfavourable outcome, as compared to South Asian subjects[8,9]. Analysis of the larger Canadian cohort of non-malignant hypertensive patients, showed that despite the higher hypertension incidence among the South Asian patients, the risk of death was lower, as compare to the White Caucasian.[29] The reasons for the ‘protective’ nature of the South Asian ethnicity are unclear as it still remains a significant favourable prognosticator after adjustment for the baseline characteristics and despite the fact that this ethnic group has high cardiovascular morbidity and mortality in general. Further more detailed research would be required to clarify the reasons for this observation.

*Limitations*

Profound heterogeneity in antihypertensive treatments used over the decades of observation, prevented us from doing statistical adjustment for changes in medications to estimate accurately their predictive role. Over the decades there have been changes in lifestyle, living and nutritional standards and these changes cannot be accounted for in this analysis. Also, the treatment and survival of cardiac patients and subjects with oncology have advanced greatly over the recent decades. Despite the fact that these cardiac or cancer conditions only cased few deaths in our population throughout the period the study, it is possible that improvements in non-antihypertensive treatments also contributed to better survival of patients with MHT more recently.

**Conclusions**

There has been a major improvement in 5-year survival in patients with malignant hypertension over recent decades. Abnormal renal function at presentation still predicts worse outcome. South Asian ethnicity is also associated with better outcomes, although mechanisms involved are yet to be established.

**REFERENCES**

1. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. The American journal of the medical sciences1974; 268 (6):336-345.

2. Ahmed ME, Walker JM, Beevers DG, Beevers M. Lack of difference between malignant and accelerated hypertension. Br Med J (Clin Res Ed)1986; 292 (6515):235-237.

3. Lip GY, Beevers M, Beevers G. The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. Journal of hypertension1994; 12 (11):1297-1305.

4. Lane DA, Lip GY, Beevers DG. Improving survival of malignant hypertension patients over 40 years. American journal of hypertension2009; 22 (11):1199-1204.

5. van den Born BJ, Koopmans RP, Groeneveld JO, van Montfrans GA. Ethnic disparities in the incidence, presentation and complications of malignant hypertension. Journal of hypertension2006; 24 (11):2299-2304.

6. Scarpelli PT, Livi R, Caselli GM, Di Maria L, Teghini L, Montemurro V, et al. Accelerated (malignant) hypertension: a study of 121 cases between 1974 and 1996. Journal of nephrology1997; 10 (4):207-215.

7. Gonzalez R, Morales E, Segura J, Ruilope LM, Praga M. Long-term renal survival in malignant hypertension. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association2010; 25 (10):3266-3272.

8. Lip GY, Beevers M, Beevers DG. Complications and survival of 315 patients with malignant-phase hypertension. Journal of hypertension1995; 13 (8):915-924.

9. Clough CG, Beevers DG, Beevers M. The survival of malignant hypertension in blacks, whites and Asians in Britain. Journal of human hypertension1990; 4 (2):94-96.

10. Leishman AW. Hypertension: treated and untreated; a study of 400 cases. British medical journal1959; 1 (5134):1361-1368.

11. Shantsila A, Lip GY. Malignant Hypertension Revisited-Does This Still Exist? American journal of hypertension2017.

12. Amraoui F, Van Der Hoeven NV, Van Valkengoed IG, Vogt L, Van Den Born BJ. Mortality and cardiovascular risk in patients with a history of malignant hypertension: a case-control study. Journal of clinical hypertension2014; 16 (2):122-126.

13. McGregor E, Isles CG, Jay JL, Lever AF, Murray GD. Retinal changes in malignant hypertension. Br Med J (Clin Res Ed)1986; 292 (6515):233-234.

14. Lip GY, Beevers M, Beevers DG. Do patients with de novo hypertension differ from patients with previously known hypertension when malignant phase hypertension occurs? American journal of hypertension2000; 13 (8):934-939.

15. Kadiri S, Thomas JO. Kidney histology and clinical correlates in malignant hypertension. East African medical journal1993; 70 (2):112-116.

16. Pitcock JA, Johnson JG, Hatch FE, Acchiardo S, Muirhead EE, Brown PS. Malignant hypertension in blacks. Malignant intrarenal arterial disease as observed by light and electron microscopy. Human pathology1976; 7 (3):333-346.

17. Shavit L, Reinus C, Slotki I. Severe renal failure and microangiopathic hemolysis induced by malignant hypertension--case series and review of literature. Clinical nephrology2010; 73 (2):147-152.

18. Li X, Zhang W, Ren H, Pan X, Chen N. Malignant hypertension complicated by acute renal failure. BMJ case reports2009; 2009.

19. DiBona GF. Sympathetic nervous system and the kidney in hypertension. Current opinion in nephrology and hypertension2002; 11 (2):197-200.

20. DiBona GF. Sympathetic neural control of the kidney in hypertension. Hypertension1992; 19 (1 Suppl):I28-35.

21. Davies DL, Beevers DG, Briggs JD, Medina AM, Robertson JI, Schalekamp MA, et al. Abnormal relation between exchangeable sodium and the renin-angiotensin system in malignant hypertension and in hypertension with chronic renal failure. Lancet1973; 1 (7805):683-686.

22. van den Born BJ, Koopmans RP, van Montfrans GA. The renin-angiotensin system in malignant hypertension revisited: plasma renin activity, microangiopathic hemolysis, and renal failure in malignant hypertension. American journal of hypertension2007; 20 (8):900-906.

23. Lip GY, Beevers M, Beevers DG. Does renal function improve after diagnosis of malignant phase hypertension? Journal of hypertension1997; 15 (11):1309-1315.

24. Amraoui F, Bos S, Vogt L, van den Born BJ. Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study. BMC nephrology2012; 13:71.

25. van der Merwe W, van der Merwe V. Malignant hypertension: a preventable emergency. The New Zealand medical journal2013; 126 (1380):39-45.

26. Gosse P, Coulon P, Papaioannou G, Litalien J, Lemetayer P. Impact of malignant arterial hypertension on the heart. Journal of hypertension2011; 29 (4):798-802.

27. Shantsila A, Dwivedi G, Shantsila E, Butt M, Beevers DG, Lip GY. A comprehensive assessment of cardiac structure and function in patients with treated malignant phase hypertension: the West Birmingham Malignant Hypertension project. International journal of cardiology2013; 167 (1):67-72.

28. Polgreen LA, Suneja M, Tang F, Carter BL, Polgreen PM. Increasing trend in admissions for malignant hypertension and hypertensive encephalopathy in the United States. Hypertension2015; 65 (5):1002-1007.

29. Quan H, Chen G, Walker RL, Wielgosz A, Dai S, Tu K, et al. Incidence, cardiovascular complications and mortality of hypertension by sex and ethnicity. Heart2013; 99 (10):715-721.

**Table 1. Characteristics of the study population**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | White Caucasian  (n=221) | African-Caribbean  (n=83) | South Asian  (n=47) | p |
| Age, years | 51±13\*† | 45±11 | 42±11 | <0.001 |
| Male sex, n (%) | 142 (64) | 51 (61) | 35 (74) | 0.28 |
| Papilledema, n (%) | 165 (75)\*† | 48 (58) | 24 (51) | 0.001 |
| Years of diagnosis, n (%) |  |  |  | 0.06 |
| *Before 1967* | 24 (83) | 3 (10) | 2 (7) |  |
| *1967-1976* | 42 (58) | 24 (33) | 6 (8) |  |
| *1977-1986* | 62 (68) | 14 (15) | 15 (16) |  |
| *1987-1996* | 40 (56) | 21 (30) | 10 (14) |  |
| *1997-2011* | 53 (60) | 21 (21) | 14 (16) |  |
| Smoking, n (%) | 129 (58)\*† | 37 (45)† | 9 (19) | <0.001 |
| Systolic blood pressure, mmHg | 231±30 | 230±25 | 221±31 | 0.12 |
| Diastolic blood pressure, mmHg | 141±20 | 147±19 | 141±17 | 0.04 |
| Serum creatinine, μmol/l | 135  [106-203]\* | 193  [128-400]† | 134  [109-171] | 0.001 |
| Left ventricular hypertrophy,  n (%) | 112 (59)\*† | 62 (84) | 33 (75) | <0.001 |
| Proteinuria, n (%) *+* | 33 (16) | 15 (20) | 11 (24) | 0.28 |
| *>+* | 105 (51) | 44 (59) | 21 (47) |  |
| Haematuria, n (%) | 44 (23) | 17 (23) | 10 (22) | 1.00 |
| Died or on dialysis | 80 (36)† | 34 (41)† | 5 (11) | 0.001 |

\* compare to African-Caribbean; † compare to South Asian.

**Table 2. Characteristics of the study population by the decades of the diagnosis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | *Before 1967* | *1967-1976* | *1977-1986* | *1987-1996* | *1997-2011* | p |
| Antihypertensive medications, n (%) | 11 (38) | 31 (43) | 26 (29) | 22 (31) | 21 (24) | 0.10 |
| Systolic blood pressure, mmHg | 230±25 | 228±28 | 228±32 | 231±27 | 229±29 | 0.94 |
| Diastolic blood pressure, mmHg | 139±22 | 147±19 | 143±22 | 140±16 | 141±19 | 0.22 |

**Table 3. Predictors of 5-year risk of death or dialysis**

|  |  |  |
| --- | --- | --- |
|  | Odds ratio [95% confidence interval) | p |
| Age (vs. <40 years) |  |  |
| *41 to 50 years* | 1.78 (0.44 - 7.17) | 0.41 |
| *51 to 60 years* | 6.12 (1.51 - 24.78) | 0.01 |
| *>60 years* | 20.6 (3.93 - 107.76) | <0.001 |
| Male sex | 1.86 (0.71 - 4.86) | 0.20 |
| Ethnicity (vs. South Asian) |  |  |
| *African-Caribbean* | 15.55 (2.06 – 117.29) | 0.008 |
| *White Caucasian* | 12.02 (1.64 – 88.15) | 0.01 |
| Malignant retinopathy | 0.73 (0.29 - 1.83) | 0.50 |
| Years of diagnosis |  |  |
| *1967-1976* | 1.07 (0.14 – 8.20) | 0.95 |
| *1977-1986* | 0.06 (0.008 - 0.43) | 0.006 |
| *1987-1996* | 0.03 (0.003 - 0.26) | 0.002 |
| *1997-2011* | 0.01 (0.001 - 0.10) | <0.001 |
| Smoking | 1.24 (0.51 - 3.04) | 0.63 |
| Systolic blood pressure | 1.01 (0.99 - 1.03) | 0.17 |
| Diastolic blood pressure | 0.98 (0.95 - 1.00) | 0.06 |
| Serum creatinine | 1.00 (1.001 - 1.005) | 0.006 |
| Left ventricular hypertrophy | 1.81 (0.67 - 4.89) | 0.24 |
| Proteinuria |  |  |
| + | 5.39 (1.41 - 20.67) | 0.01 |
| >+ | 4.70 (1.52 - 14.57) | 0.007 |
| Haematuria | 1.13 (0.36 - 3.55) | 0.90 |
| Use of antihypertensive medications | 1.91 (1.26 - 2.90) | 0.002 |

**Figure legends:**

Figure 1. Study analysis flow chart.

**Figure 2. Rates of 5-year mortality in patients with malignant hypertension diagnosed in different time periods**



**Figure 1.**

****

**Figure 2.**