Original Article

Characteristics and Outcome of Biopsy-proven Malignant Hypertension with Severe Kidney Injury: A Retrospective Study

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Abstract

Background: Although malignant hypertension begets multiple target organ damage, there is limited data on patients with severe renal injury and evident malignant hypertension in renal histopathology. **Methods:** We assessed the baseline demographic, histopathological findings and clinical outcomes in this retrospective analysis of patients with biopsy-proven malignant hypertension. **Results:** Thirty cases were analysed, the mean age of patients was 40 ± 11.5 years, 28 (93.3%) were males and the average systolic and diastolic blood pressures at hospitalisation were 197.04 ± 24.14 and 117.41 ± 18.31 mmHg, respectively. Severe retinopathy was seen in 10 (33.3%). The median eGFR at admission was 6.3 (IQR 4.4–9.15) mL/min and 21 (72.4%) needed dialysis. Nine (30%) cases with glomerular crescents were having the primary glomerular disease (7 IgAN, 1 C3 glomerulonephritis, 1 membranoproliferative glomerulonephritis) and 17 (56.6%) had thrombotic microangiopathy. Three-month ESRD free survival was 34.5% (n = 10) and the ESRD cohort had more incidence of dialysis requiring kidney injury at presentation (94.4% vs. 40% in the non-ESRD cohort). Patient survival at 1 year was 50%. Isolated malignant hypertension, differed from others with regard to lesser incidence of severe retinopathy, less glomerular sclerosis (29.61 ± 15.86 vs. 48.45% ± 30.78; P = 0.03), absence of crescents (P = 0.02), more incidence of tuft wrinkling (100% vs. 35%, P = 0.00) and total vessel occlusion (P = 0.02). **Conclusion:** Clinicopathologically, accelerated essential hypertension differs from hypertension of glomerular disease. Degree of kidney injury at presentation is risk predictor for long-term morbidity in malignant hypertension.

Keywords: *Creatinine, crescent, fibrinoid, malignant hypertension, outcome*

Introduction

Malignant hypertension has a low prevalence in the general population.[1,2] An exact definition has been waved aside till date. Most recently it was defined as the presence of very high blood pressures (no cut off value) with ischaemic target organ damage (retina, kidney and heart or brain) and so, has digressed from banking on ischaemic retinal changes which can be variably present.[3,4] Renal abnormalities including elevated serum creatinine, proteinuria (often ≤1 g/24 h) and microscopic haematuria are seen in 60–70% and impaired renal function portends poor renal and patient survival.[5]

Malignant hypertension-related renal changes, thrombotic microangiopathy (TMA) and kidney function often recover upon blood pressure control.[6,7] Although these acute lesions may proceed to heal, the hypertensive state induces damage to large and medium-sized vessels facilitating atherosclerosis and fibrous intimal hyperplasia.[8] At presentation, 18–40% may require renal replacement therapy (RRT) and over the long term, 6–46% have culminated in end-stage kidney disease (ESKD) with a patient survival rate of 84–90%.[2,5,9-12] Death often results from cardiovascular events.[5,11,12] Survival of malignant hypertension has considerably improved with the advent of antihypertensive therapy, but the end-stage kidney disease (ESKD) remains a significant cause of morbidity and mortality.[9,13,14] Initial serum creatinine and control of hypertension were the primary determinants of renal outcome and patient survival.[5,15] There is only limited information on the clinicopathological profile, renal outcome and patient survival in biopsy-proven malignant hypertension, especially in the current era of potent antihypertensive medications. In most of the existing data, the definition of

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malignant hypertension is clinical, with emphasis on retinal changes rather than the presence of fibrinoid necrosis on histology. The current study looks into the long-term outcomes of malignant hypertension and its clinical and renal histological correlate.

Materials and Methods

Setting and study participants

This study is a retrospective cohort study done in the department of nephrology in a tertiary care hospital. The electronic medical records from January 2014 to June 2018 were screened to identify patients with a histopathological diagnosis of malignant hypertension in the 'final diagnosis' section of the renal biopsy report. Patients who had incomplete baseline clinical information or previously documented chronic kidney disease (CKD) were excluded from the study. The histopathology slides were retrieved and reviewed by a single pathologist, blind to the clinical data. A total number of 34 cases with a histological diagnosis of malignant hypertension were identified; four were excluded due to incomplete data.

Data source and bias

The clinical data and investigations were retrieved and entered into a predefined proforma. Age, presenting symptoms, duration of hypertension, co-morbidities, baseline laboratory parameters, fundus examination, echocardiography, renal histopathology and treatment received were documented from hospital records. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) 2009 creatinine equation. The follow-up information was retrieved from outpatient records. Patients were contacted over the phone for additional information, if required.

Definitions

Malignant hypertension was defined in renal biopsy by findings of small vessel fibrinoid necrosis, thrombi, intimal mucoid change, glomerular thrombi and/or TMA in the acute phase or ischaemic wrinkling, periglomerular fibrosis and/or onion skinning in the chronic phase. Intimal fibrosis, hyalinosis, and medial hyperplasia were also included as chronic changes.[16] Rapidly progressive renal failure as evidenced by the doubling of serum creatinine from baseline within few weeks to months. Peripheral TMA was defined as thrombocytopenia (platelet count $<150 \times 10^9$/L) together with either an elevated lactate dehydrogenase (LDH ≥220 U/L) or the presence of schistiocytes on peripheral smear. Hypertensive retinopathy was defined by the modified classification system (Mitchell-Wong) as mild – retinal arteriolar narrowing related to vasospasm, arteriolar wall thickening or opacification, and arteriovenous nicking, referred to as 'nipping'; moderate – haemorrhages, either flame or dot-shaped, cotton-wool spots, hard exudates and microaneurysms; and severe – some or all of the above, plus optic disc oedema.[17]

Histopathology specimens where more than 50% of the glomeruli were viable and had not shown any features of primary glomerular diseases (cellularity, thickening, expansion and non-vascular immune deposits) were considered an accelerated phase of essential hypertension and were labelled as isolated malignant hypertension. Histology with significant glomerulosclerosis, interstitial fibrosis, tubular atrophy, and non-specific immunofluorescence where the primary disease could not be determined were just labelled as having CKD. ESRD was defined as the patient on maintenance dialysis.

Statistical methods

Data were checked for normality of distribution using the Kolmogorov-Smirnov test. Data were expressed as mean +/- standard deviation (SD) when normally distributed and as the median and interquartile range (IQR) when distribution was skewed. Frequencies and percentages were given for categorical variables. Between-group differences were assessed by the student's *t*-test for parametric and Mann-Whitney U test for non-parametric distributions. Chi-square analysis was used for categorical variables. All *P* values were two-tailed, and a $P < 0.05$ was considered statistically significant. All analyses were performed using statistical package for the social sciences (SPSS) 21.0 software for Windows (SPSS Inc., Chicago, IL, USA)

Results

A total of 1180 renal biopsies from January 2014 to December 2018 were screened, 34 (2.9%) of them histopathologically diagnosed as malignant hypertension were identified. Four biopsies were excluded because of incomplete clinical data. Table 1 shows the demographic and clinical parameters at admission. Dialysis at admission was required by 21 (72.4%) subjects.

Pathological findings

The proportion of sclerosed glomeruli averaged 42.6 ± 28.2%. Crescents were seen in nine (30%) biopsies and five (20%) had crescents in more than 25% of the glomeruli. All those who had crescents had biopsy evidence of underlying primary glomerular disease (7 IgA nephropathy, one C3 glomerulonephritis, and one membranoproliferative glomerulonephritis). The other prominent glomerular findings were ischaemic wrinkling in 15 (55.2%), periglomerular fibrosis in 10 (34.5%), mesangial matrix expansion in 14 (48.3%) and mesangial hypercellularity in 15 (51.7%). The data on histopathological changes are provided in Table 2. Acute arterial or arteriolar TMA was more frequent than glomerular TMA (n = 16 [55.2%] vs. 1 [3.4%]), and systemic TMA was uncommon (n = 2). Prominent changes in the small vessels were fibrinoid necrosis in 22 (73.3%)

Table 1: Baseline parameters at initial admission

Variables	Statistics
Age (years)	40±11.5
Male Gender	28 (93.3%)
Systolic blood pressure (mmHg)	197.04±24.14
Diastolic blood pressure (mmHg)	117.41±18.31
Oliguria	15 (50%)
Past co-morbidities	
Hypertension	12 (41.4%),
Diabetes mellitus	5 (17.2%)
Smoking	12 (41.4%)
Need for dialysis at presentation	21 (72.4%)
Hypertensive retinopathy	
Mild	11 (40.7%)
Moderate	7 (25.9%)
Severe	10 (38.5%)
LV hypertrophy*	14 (93.3%)
Serum albumin (g/dL)	3.1±0.5
Serum potassium (mEq/L)	4.3±0.8
Serum creatinine (mg/dL)†	9.1 (7.2-10.75)
eGFR (mL/min)†	6.3 (IQR 4.4-9.15)

* missing cases-15, † median with interquartile range

and thrombi in 15 (50%). In the large vessels, intimal mucoid change, intimal fibrosis and medial hyperplasia were evident in 11 (36.7%), 16 (55.2%) and nine (30%), respectively. Seven cases (29.3%) had vessel wall immune deposits in the form of C3, IgG or IgM. Acute and chronic lesions were present in 29 (96%) and 25 (83.3%) cases respectively.

Isolated malignant hypertension

Histopathology specimens where more than 50% of the glomeruli were viable and had not shown any features of primary glomerular diseases (cellularity, thickening, expansion, non-vascular immune deposits) were analysed as isolated malignant hypertension (9/30; 30%) [Table 3]. The isolated malignant hypertension group had less incidence of severe retinopathy. Crescents were conspicuously absent in this group versus 0 to 17 crescents in 9 cases of latter group (P = 0.02); and the percentage of sclerosed glomeruli were also significantly less (29.61 ± 15.86% vs. 48.45% ± 30.78; P = 0.03). Other tubulointerstitial and vascular changes were of similar frequencies. Although there was significant total vessel occlusion by concentric hyperplasia, there was no evidence of large vessel stenosis in carotid or renal Doppler. Chronic and active lesions were similar compared to the other cases of renal parenchymal hypertension (88.9% vs. 100% acute lesions; 77.8% vs. 85.7% chronic lesions).

Long-term outcomes

Renal survival

Follow-up data until 3 months was available for 29 patients. At the end of 3 months, 19 (65.5%) patients progressed to

Table 2: Histopathological findings

Parameter	Value
Number of glomeruli†	13 (9.5-20)
Percentage of sclerosed glomeruli	42.6±28.2
Crescents in biopsy	9 (30%)
Endocapillary cellularity	4 (13.8%)
Glomerular basement membrane thickening	4 (13.8%)
Ischaemic wrinkling	15 (55.2%)
Periglomerular fibrosis	10 (34.5%)
Mesangial expansion	14 (48.3%)
Mesangial cellularity	15 (51.7%)
Intimal fibrosis	16 (55.2%)
Arteriosclerosis	4 (13.3%)
Thrombotic microangiopathy	16 (55.2%)
Acute tubular necrosis	10 (34.5%)
Interstitial fibrosis	
Mild	4 (13.8%)
Moderate	5 (17.2%)
Severe	1 (3.4%)
Tubular atrophy	
Mild	07 (24.1%),
Moderate	12 (41.4%)
Severe	8 (27.6%)
Diagnosis	
IgA Nephropathy	8 (26.7%)
Diabetic kidney disease	3 (10%)
Isolated malignant hypertension	9 (30%)
Chronic kidney disease	5 (16.7%)
Others	1 each of Acute interstitial nephritis, MPGN, C3GN, pyelonephritis, mesangioproliferative glomerulonephritis.

† median with interquartile range

ESRD. Among the remaining 10 patients, eight (27.5%) showed progressive improvement in eGFR and two showed a declining trend. Only one patient who had eGFR of 46 mL/min at the initial presentation had a recovery to eGFR >60 mL/min. The characteristics of the patients with and without renal survival are shown in Table 4. Crescents were absent in 70% of non-ESRD and 63% of ESRD cases, and in the ESRD group (n=19), 6 had crescents in 15%–100% of the glomeruli. On univariate analysis, the severity of renal failure at presentation (serum creatinine, eGFR, dialysis requiring kidney injury) turned out to be the only factor affecting renal survival. The renal survival was similar in patients with isolated malignant hypertension compared to those with glomerular pathologies (4 of the 9 vs. 15 of the 20; P = 0.20).

Patient survival

Only 26 patients had follow-up data beyond 1 year (16 patients with ESRD and 10 without ESRD). The

Table 3: Comparison of factors between the groups of isolated malignant hypertension vs. other diagnoses

	Isolated Malignant hypertension (*n* = 9)	Others (*n* = 21)	*P*-value
Age (years)	41.44±5.74	39.38±13.25	0.55
Smoking	2/7	11/18	0.20
eGFR (mL/min)	7.6±4.3	9.97±8.91	0.49
Hypertensive retinopathy	5/9	13/18	0.42
Neuroretinopathy	1/9	9/17	0.08
Percentage of sclerosed glomeruli	29.61±15.86	48.45% ± 30.78	0.03
Percentage of Crescents	0	0-100%	0.02
Endocapillary cellularity	0/9	4/20	0.28
Ischaemic wrinkling	9/9	7/20	0.00
Periglomerular fibrosis	5/9	5/20	0.20
Mesangial expansion	2/9	12/20	0.10
Thrombotic microangiopathy	4/9	12/20	0.68
Acute tubular necrosis	5/9	5/20	0.20
Total vessel occlusion	4/9	1/20	0.02

Table 4: Analyses of clinical and pathological factors between ESRD (*n* = 19) vs. non-ESRD groups (*n* = 10)

Parameters	Non-ESRD (*n* = 10)	ESRD (*n* = 19)	*P*-value
Age	39.20±10.59	40.37±12.43	0.80
Past hypertension	6/10 (60.0%)	6/18 (33.3%)	0.243
Smoker	44.4%	53.3%	1.00
Serum creatinine at presentation	6.32±2.49	10.92±4.11	0.005
eGFR at presentation	13.31±9.89	6.45±4.62	0.07
Dialysis at onset	4/10 (40.0%)	17/18 (94.4%)	0.003
Severe retinopathy	22.2%	50.0% (8/16)	0.229
% sclerosed glomeruli	40.58±18.41	41.13±31.53	0.96
Crescents in biopsy	4/10	6/18	0.60
Ischaemic wrinkling	6/10 (60.0%)	9/18 (50.0%)	0.70
Periglomerular fibrosis	4/10 (40.0%)	6/18 (33.3%)	1.00
ATN	5/10 (50%)	4/18 (22.2%)	0.21
Interstitial fibrosis	4/10 (40%)	6/18 (33.3%)	0.59
Tubular atrophy	9/10 (90%)	17/18 (93.5%)	0.08
Thrombotic microangiopathy	6/10 (60%)	9/18 (50%)	0.70
C3 immune deposits	1/9 (11.1%)	5/16 (31.2%)	0.40
Vascular immune deposits	3/10 (42.9%)	4/18 (57.1%)	1.00
Final diagnosis*	Mal HTN 5, IgAN 3, DN 1, CKD 0	Mal HTN 4, IgAN 5, DN 2, CKD 4	0.42

*Mal HTN- more than 50% of the glomeruli were viable and had not shown any features of primary glomerular diseases (cellularity, thickening, expansion, and non-vascular immune deposits) hence considered as an accelerated phase of essential hypertension, IgAN- IgA Nephropathy, DN- Diabetic nephropathy, CKD- Histopathology specimens with significant glomerulosclerosis, interstitial fibrosis, tubular atrophy, non-contributory immunofluorescence and thence primary disease could not be determined labelled as chronic kidney disease

overall 1-year patient survival was 50% (13/26). Eleven deaths happened in the ESRD cohort and two deaths in the non-ESRD cohort (P = <0.005). Those who died had severe hypertensive retinopathy at presentation (11/13 vs. 4/13; P = 0.005). The renal TMA lesions were not different between the survivors and non-survivors (9/13 vs. 6/13; P = 0.23). In most cases, the exact cause for death could not be delineated as it happened outside the confines of the hospital. The survival group had more incidence of IgAN (5 vs. 1) and isolated malignant hypertension (7 vs. 1) with less of diabetic nephropathy (0 vs. 3) or undetermined CKD (0 vs. 5) (P = 0.001).

Discussion

Malignant hypertension is rarely seen beyond the fifth decade and also rarely reported below the age of 35 years, and our cohort had a wide age range of 18 to 65 years (mean 40 ± 11.5 years), with the maximum number of patients being in 35–60 years group.[1,5,18] In contrast to previous literature, the high proportions of dialysis requiring renal failure (72%) might be due to many with rapidly progressive renal failure, with biopsy-proven malignant hypertension.[9,5,19] To our knowledge, patients with this severe degree of renal failure with biopsy-proven malignant hypertension have not been studied till date.

Despite biopsy evidence of malignant hypertension, severe neuroretinopathy was confined to only one-third of the patients thereby questioning the reliability of fundal changes as the hallmark of malignant hypertension.[4,20,21] In a retrospective analysis, severe retinopathy was documented in less than 50% of cases with accelerated hypertension.[22]

In cases of renal TMA, the pathology was almost always arterial or arteriolar than glomerular; a feature documented previously in a large study involving 61 cases of biopsy-proven malignant hypertension-induced TMA.[23] Peripheral TMA was less often seen even when there was evidence of the same in target organs. The significant correlations of fibrinoid necrosis, proliferative endarteritis, arteriolar hyalinisation or myxoid intimal thickening with the levels of hypertension evidenced in previous studies were lacking in this cohort.[24-26] Fibrinoid necrosis in vessels has been associated with uncontrolled hypertension and death.[27]

There is not too much literature on malignant hypertension patient profile and the detailed renal pathological descriptions are before the 1990s. The classical renal histopathology description of malignant hypertension includes glomerular fibrinoid necrosis, mesangiolysis, endothelial swelling, tuft collapse, ischaemic wrinkling, and vascular changes of fibrinoid necrosis, arteriolar hyalinisation and thrombus and mucoid intimal hyperplasia.[16] The same has been the findings in several clinicopathological studies but findings were variable in each cohort.[27-29] Arteriolar hyalinisation, vascular fibrinoid necrosis and mucoid intimal thickening were universally reported, whereas glomerular fibrinoid necrosis is exceedingly rare.[27-29] One notable feature among blacks was the absence of arteriolar fibrinoid necrosis.[29] This was also noted in the Japanese series of 12 patients where onion skin lesions and tuft collapse was seen in all in the absence of fibrinoid necrosis. In the current study, there is 100% arteriolar/arterial involvement with a predominance of arteriolar/arterial fibrinoid necrosis, acute vascular TMA, intimal fibrosis and intimal mucoid changes with the sparse incidence of glomerular fibrinoid necrosis and arteriolar hyalinisation. Small vessel fibrinoid necrosis and thrombi are the prominent findings in our cohort though are not universal.

Although we excluded patients with pre-existing documented CKD, the majority of the patients turned out to have chronic changes in renal pathology. The chronicity in the glomeruli may have been either due to long-standing hypertension or due to undetermined pre-existing CKD. One-third of the patients were found to have crescents. As noted above, crescent may be the cue to a glomerular disease-causing hypertension while ischaemic wrinkling and total vessel occlusion were conspicuous in isolated malignant hypertension. In the unique detailed description of pertinent histopathology by Hepinstall, malignant transformation of essential hypertension differed from those secondary to glomerulonephritis in tuft necrosis, focal involvement of glomeruli, arterial necrosis (with less than 5% of vessels involved) and endarteritis fibrosa in the small arteries.[26]

The hypertensive retinopathy of severe grades was seen in only 33.3% (n = 10) cases and only in one case of isolated malignant hypertension. It was more commonly seen in cases of malignant hypertension with evidence of primary glomerular disease and was negatively associated with glomerular ischaemic wrinkling. This was impressively documented in a previous study where hypertensive retinopathy of all grades occurred more frequently in renal parenchymal hypertension than in essential hypertension ($P < 0.01$). Severe hypertensive retinopathy was seen even in mild hypertension of renal parenchymal disease and was attributed to the increased local vascular permeability and intraretinal leakage of plasma components due to the uremic toxins.[30] Severe retinopathy was also an indicator for non-recovery of renal function, and along with renal dysfunction indicates multiple target organ damage and thence poor renal and patient outcomes.[22]

Recovery of renal function is often incomplete when there is biopsy evidence of malignant hypertension and this is further compromised when kidney injury is severe.[5,6,7,9,15] However, even partial renal recovery seems to augur good patient survival. The Bordeaux registry of malignant hypertension, though incomparable about the acute kidney injury (AKI) severity, had noticed worsening of renal function in 14% at 48 months.[12] Successful therapy with antihypertensives do bring about notable histopathological changes with regression of necrosis and appearance of subintimal fibroplasia.[8] As the degree of kidney injury was severe in our cohort the outcomes are not comparable to the existing data on malignant hypertension outcomes.

ESRD rate in malignant hypertension was high at 65.5% and again the severity of kidney injury at presentation determined the long-term renal outcome while none of the acute or chronic vascular changes presaged ESRD.[5,10,12] The presence of TMA also did not predict the long-term renal outcome. This is similar to the large retrospective analysis (1974–2007) wherein those with worse baseline renal function (serum creatinine >3.4 mg/dL), 83.3% finally needed maintenance dialysis.[5] The long-term renal outcome of biopsy-proven malignant hypertension had shown progression to ESRD in 33% even in cohorts with lesser degrees of AKI (serum creatinine 2.27 [1.74-3.14] mg/dL) at presentation.[10,11,23] In contrast, only 3% of patients with severe non-malignant hypertension develop ESRD in long term.[31] Apart from the serum creatinine factor, uncontrolled blood pressure also increases the risk of ESRD by 4–5 folds.[11] Our study also affirms that the severity of renal failure at presentation is the detrimental prognostic factor for renal survival.

The death rate was 50% (n = 13) and the prime predictor was ESRD. Multiple target organ damage primarily renal failure and cardiovascular events are the predictors of death in malignant hypertension, and the survival rate without ESRD is found to be 90% at 5 years.[9-11,32] There is an increased risk of death in malignant hypertension with every target organ damage (heart, kidney, retina) and severe retinopathy has been associated with mortality.[32] Interestingly, the absence of hypertensive retinopathy was also linked to patient survival in our cohort and this could be analysed further in future studies. The lesser incidence of baseline mild to moderate hypertensive retinopathy, glomerular endocapillary cellularity and tubular atrophy in those who had survived could have been the positive factors for lesser rates of ESRD in these cases.

The two large retrospective analyses of 30 years and 17 years which included 315 and 120 patients with malignant hypertension and follow-up of 1–389 months and 28–108 months, respectively, the renal outcome and patient survival were associated with serum creatinine (>200 μmol/L and 175 μmol/L) and uncontrolled hypertension. The follow-up data was of a very long term and the renal dysfunction in the majority of subjects was not severe at presentation (175 (104–402) μmol/L or 1.2–4.5 mg/dL).[10,11] In this respect, our study has included only those with severe renal dysfunction with biopsy-proven malignant hypertension and thorough data in this type of cohort is lacking.

Strengths and limitations

Strengths include the contribution of clinically relevant and previously unavailable data on clinicopathological features, renal outcome and patient survival of an unselected, well-described and a relatively large cohort of patients with renal biopsy-proven malignant hypertension. Limitations include its retrospective nature and the possibility of coding errors. A separate analysis could not be performed for patients with primary glomerular diseases because of the limited number of patients. The association between serum creatinine, renal recovery and patient survival is reiterated. Whether malignant hypertension associated TMA is purely arterial or arteriolar or whether the ischaemic wrinkling with total vessel occlusion always indicate isolated malignant hypertension (accelerated essential hypertension) not due to a primary glomerular disease are the points to ponder.

Conclusion

Malignant hypertension is an important cause for rapidly progressive renal failure and clinical description should be all-inclusive of target organs beyond the retina. Vascular microangiopathy and small vessel fibrinoid necrosis were prevalent. The accelerated essential hypertension differs from renal parenchymal hypertension in histology. As in other causes of renal injury, the initial serum creatinine is the principal determinant of renal outcome in cases of severe kidney injury of malignant hypertension. Recovery is often incomplete, and eventually, renal recovery determines patient survival.

Compliance with ethical standards

Procedures followed were following the ethical standards of the Institutional Review Board (IRB)/Ethics Committee (No. JIP/IEC/2019/552).

Declaration of patient consent

Informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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