



Outcome of Haematological and Haemostatic Indices in Hospitalized Yellow Fever Patients at the Centre for Communicable Disease Control and Research (CCDCR) Federal Medical Centre, Asaba, Delta State, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To assess the outcome of haematological and haemostatic indices in hospitalized Yellow Fever Positive patients treated using levels of full blood count, platelet count and other red cell indices at the Centre for Communicable Disease and Research (CCDCR) Federal Medical Centre, Asaba, Delta State, Nigeria.

Study Design: Retrospective observational study.

Place and Duration of Study: Centre for Communicable Disease Control and Research (CCDCR), Federal Medical Centre Asaba, Nigeria, between August and December 2020.

Methodology: Descriptive data was collected from the records of fifty-six (56) patients aged 16 – 65 years who were hospitalized and treated at the CCDCR FMC Asaba, within the months of August to December, 2020 and 56 non-Yellow Fever subjects as control subjects. The patients' samples were previously collected and analyzed for haematological parameters (neutrophil, eosinophil, basophil, lymphocytes, monocytes, platelet count, mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC), using an automated haematology analyzer. Data collected was analyzed using SPSS version 25 and P values less than .05 were considered statistically significant.

Results: There were higher levels of total white blood cell count, eosinophil and MCH in hospitalized yellow fever patients when compared with the control group ($P < 0.05$). On the other hand, there was a lower level in platelet count of hospitalized yellow fever patients when compared with non-yellow fever control subjects ($P < 0.05$). There was no significant difference in other haematological indices assayed which appeared normal ($P > 0.05$).

Conclusion: In conclusion, it can be inferred that yellow fever can be associated with several haematological derangements which this study has succeeded to lay bare. Understanding these characteristics aids in planning therapy, management of patients as well as monitoring outcome.

Keywords: Haematological indices; hospitalized yellow fever positive patients; Centre for Communicable Disease Control and Research (CCDCR); Federal Medical Centre; Asaba; Delta State; Nigeria..

1. INTRODUCTION

Yellow fever virus (YFV) an enveloped RNA virus belongs to the genus *Flavivirus*. Its family is *Flaviviridae* and the Order *Amarillovirales*. The positive-sense, single-stranded RNA is around 10.862 nucleotides long and has a single open reading frame encoding a polyprotein [1].

The mature YFV virions are icosahedral, with a nucleocapsid made up of capsid (C) protein subunits and a lipid bilayer produced from host membranes surrounding it. Envelope (E) glycoprotein and membrane (M) protein dimers are embedded in the viral envelope. The virion has a diameter of around 40 nm with surface projections of 5 to 10 nm. The E glycoprotein is the most important component of the virion surface, and it is responsible for the majority of biologic activity, including cell-surface receptor binding, virion assembly and fusion activity at low pH, and immunogenicity [2,3]. After the virus infects a host cell, a single polyprotein of the YFV is produced, signaling the start of viral genome translation. The host's YFV proteases break the protein, resulting in viral proteins that are required for virus genome replication and virion generation [4].

Yellow fever (YF) disease which is caused by the yellow fever virus, is transmitted and spread mainly to humans and non-human primates through bites from infected female mosquitoes of

the *Aedes specie* across Africa and America, as well as *Haemagogus spp.* vectors across Sub-Saharan Africa [5]. Estimates show, however, that YF continues to affect over 200,000 persons annually in tropics, with at least 30,000 fatalities [6]. The current YF endemic zone covers 44 nations in Africa, South and Central America, with about 900 million individuals at risk of infection [7]. This total includes an estimated 508 million people in 32 African countries, and the remainder in 12 South and Central American countries [8].

Yellow fever has a wide clinical spectrum, ranging from asymptomatic or moderate infection to potentially lethal acute bleeding and jaundice [9]. Yellow fever is suspected based on the patient's clinical symptoms, places and times of travel (if the patient comes from a non-endemic country or area), activities, and the epidemiologic history of the suspected infection location. Nonetheless, laboratory testing is required for definitive diagnosis and case confirmation [10]. Yellow fever is a febrile sickness that produces hepatic, renal, and cardiac abnormalities. Internal hemorrhage, kidney failure, shock, coma, or even death can occur in more serious situations [11]. The mortality rate in the most severe instances is between 20 and 50 percent [12].

One of the targets for viral replication is the kidney tissues. Maciel et al. [13] described in

details the kidney lesions observed in hepatocyte destruction with steatosis, apoptosis, and necrosis, primarily in the mid zonal region of the liver, as a hallmark of yellow [14]. Because the liver parenchymal cells produce the majority of coagulation factors, anticoagulant proteins, and fibrinolytic system components, alterations in hepatic functioning will result in derangement in haemostatic indices. Abnormal haemostatic mechanisms arising from abnormal liver function can occur for a variety of causes, including decreased coagulation factor synthesis, coagulation factor consumption, altered clearance of activated coagulation factors, and quantitative and qualitative platelet abnormalities [15].

Autopsies carried out on patients affected by the severe form of yellow fever virus infection, showed disseminated mycoses. Additionally, according to the study by Maciel et al. [13], interstitial nephritis was noted, with associated tubular necrosis and interlobular thrombosis in kidney vessels. There was also hemorrhage and ischemic necrosis of the adrenal gland. According to Hoffbrand and Moss [16], the kidney is crucial for the production of the hormone erythropoietin, which is involved in erythropoiesis. If the kidney is compromised, as it is in YF, red blood cell production would be impeded, resulting in anaemic conditions.

Haemostatic indices are widely used in the monitoring and management of treatment in a variety of health conditions, including YFV infection. YFV infection has been linked to haemostatic dysfunction, including blood cell depletion, severe bleeding with petechiae ecchymoses, epistaxis, haematemesis, and multiorgan damage including liver disease, renal failure, vascular and endothelial damage, and cardiac failure with shock. Because the liver synthesizes the bulk of coagulation proteins, inhibitors of coagulation, and fibrinolytic system, liver injury predisposes the patient to coagulation problems. This, in turn, can lead to high levels of proinflammatory and anti-inflammatory cytokines the effect of which results to compromised immune network and further worsens patients' response to treatment. Hemostatic indicators require constant monitoring and prompt intervention. As a result, it is hoped that the findings of this study will aid in understanding and monitoring the progression of cell disorders and coagulation instability in YF positive patients, as well as supporting the use of these indices in patient management and in making useful prognosis.

Unfortunately, there is little knowledge on how YFV infection affects haematological and hemostatic indices in Nigerian patients, particularly in Delta state. As a result, the goals of this research are to determine the characteristics of hemostatic parameters in hospitalized YFV positive patients, how the infection affects these indices in patients of Nigerian descent, specifically patients treated in Delta State, and how the results of these indices can be used to plan therapy and monitor treatment. The focus of this research is therefore to evaluate the haematological and hemostatic parameters of YFV-infected patients hospitalized at the Centre for Communicable Disease Control and Research (CCDCR) Federal Medical Centre Asaba, Delta State.

2. MATERIALS AND METHODS

2.1 Description of Study Area

The study area for this work is Centre for Communicable Disease Control and Research (CCDCR), Federal Medical Centre (FMC), Asaba, Delta State, Nigeria, as a single-center study. Federal Medical Centre which was established on 12th August 1998 is located in the central area of Asaba metropolis, the capital city of Delta State.

The CCDCR was established in 2020 in consonance with the Nigerian Centre for Disease Control (NCDC) and World Health Organization (WHO) guidelines for treatment of infectious/communicable diseases. The treatment center is completely upheld by the management of Federal Medical Center in conjunction with the Delta State government. The Centre has an exceptional laboratory and groups of qualified staff in the medical field who are competent in the management of patients with Yellow Fever virus.

2.2 Study Population

The study population consists of all the patients, both male and female that presented at the accident and emergency unit of Federal Medical Centre, Asaba during the outbreak who tested positive to the Yellow Fever virus and were admitted into the Centre for Communicable Disease Control and Research (CCDCR) of the hospital afterwards. Data of 56 patients aged 14-65years admitted into the Centre for Communicable Disease Control and Research (CCDCR), Federal Medical Center, Asaba, Delta

State in the months of August – December, 2020 was collected. 56 non- Yellow Fever patients were also recruited into the study as control subjects. Laboratory findings of their haematological indices as well as demographic profile of the patients were the data collected.

2.3 Selection Criteria

2.3.1 Inclusion criteria

Male and female patients (14 – 65years) who tested positive to yellow fever virus at Federal Medical Centre, Asaba and were admitted and treated in the Centre for Communicable Disease Control and Research (CCDCR).

2.3.2 Exclusion criteria

Patients who tested positive to yellow fever virus in Federal Medical Centre, Asaba, but were not admitted into the hospital's CCDCR were excluded from the study. Also, patients that were treated in other hospitals and referred to the facility were excluded from the study. Additionally, patients whose required information are incomplete both in their case note and the laboratory register were excluded from the study.

2.4 Data Collection and Analysis

2.4.1 Data collection

Data of 56 yellow fever patients admitted into CCDCR of Federal Medical Centre Asaba, Delta State in the months of August -December, 2020 was collected and those of 56 non-yellow fever subjects were also collected. Data collected included demographic profile, and laboratory findings of their haematological indices.

2.4.2 Sample analysis

2.4.2.1 Estimation of Full Blood Count, Red Cell Indices and Platelet Count using BC-5000 auto haematology analyzer model manufactured by Shenzhen Mindray Bio - medical Electronics Co. Ltd

Full blood count of all participants in this study was carried out using the Mindray BC -5000 5-part differential Auto haematology analyzer. The measurement methods used in this analyzer are, the Electrical Impedance method for determining the red blood cell (RBC) and Platelet (PLT) data, the colorimetric method for determining the hemoglobin, flow cytometry by laser for determining the white blood cell data. Other

parameter results including the red blood cell indices (MCV, MCH, MCHC, RDW) were obtained through automated calculation.

2.5 Statistical Analysis

The Statistical Package for Social Sciences Software (SPSS) version 25 was used to analyze the data. Continuous variables are shown as mean and standard deviation, whereas categorical variables are displayed as frequencies and percentages in tables and student's t-test was used to analyze differences in mean values of the two groups groups. P – value less than .05 was statistically significant. Spearman's correlation method was applied in determining relationship.

3. RESULTS AND DISCUSSION

Diagnosis of yellow fever infection is based on travel history to an endemic area, vaccination history, exposure to infected mosquitoes, symptoms at presentation as well as laboratory findings [17]. It has been established that yellow fever in man is an acute infection which most of the time vary in severity from a subclinical to a rapidly fatal disease. Hence, the disease outcome may be survival followed by development of permanent immunity or death. Approximately 15% of symptomatic patients will develop severe disease among which 30% to 50% will die [17]. The experience in our centre follows this pattern as 54% of the hospitalized symptomatic yellow fever patients died from the complications of the infection.

Yellow fever is a viral haemorrhagic fever caused by a flavivirus. About 15% of individuals infected by yellow fever virus progress to the third stage of the disease known to be characterized by multiple organ damage such as hepatic, renal, and cardiac abnormalities linked to high levels of proinflammatory cytokines which culminates to the dysfunction of these organs [11,17]. It is only to be expected that this organ dysfunction will disrupt the entire tightly coordinated body physiological processes, the haematopoietic and haemostatic mechanisms inclusive.

Haematological and haemostatic indices have been applied as an indispensable tool in assessing and monitoring disease progression and response to treatment in yellow fever infection. It has been well established that many haematological and haemostatic abnormalities occur in yellow fever infection possibly due to cell

distortions that occur following inflammation. This inflammation could be caused by the infection which may likely result to aberrant production of both haematological precursor cells and haemostatic proteins owing to disruption in liver functions associated to liver damage as the liver has indisputable influence on several essential functions of many organs in the body, the haematopoietic system inclusive [17]. The liver in addition to playing an essential role as extravascular haematopoietic organ in early foetal life and bone marrow infiltrative disease, also synthesizes and stores many of the elements and proteins necessary in blood production. In addition, it plays a critical role in haemostasis [18]. Derangement in some of these indices have been associated with poorer disease outcome or even mortality [19]. Crochemore et al. [17] in their study demonstrated that higher levels of leukocytes and neutrophils were associated with poorer disease outcome and even death. Although we could not establish a relationship between haematological indices and mortality in our study due to deficiencies in available information, difference in some of these indices was established between that of the study group and apparently healthy individuals, also among the

study groups based on age, gender and mortality.

In this study, we evaluated the difference between the haematological and haemostatic indices of symptomatic yellow fever patients admitted in our Centre and that of apparently healthy individuals as well as comparing the results of the study group based on age, gender and mortality (survival).

As illustrated in Table 2, showing comparison of mean levels of packed cell volume, total white blood cell count, neutrophil, lymphocyte, eosinophil, monocyte, platelet, MCH, MCHC, MCV, HB and basophil of the study population and apparently healthy individuals (controls), the levels of packed cell volume, neutrophils, lymphocytes and monocytes did not differ significantly ($p > .05$) between yellow fever infected patients and the control group. This could possibly be due to the stage of the disease as well as prompt intervention proffered by medical experts upon hospitalization of yellow fever patients in CCDCR, Federal Medical Centre Asaba. Related to these arguments is the critique that a small sample size could contribute to the result obtained in this study.

Table 1. Basic characteristics of subjects

Variables	Frequency n=56	Percentage (%)
Sex		
Male	44	78.6
Age group		
Female	12	21.4
< 20years	23	41.1
> 20years	33	58.9
Age (Mean±SD)	26.52±12.94	

Table 2. Haematological indices in Yellow Fever positive patients and apparently healthy individuals (controls)

Parameter	Mean value (Control)	(Yellow Fever positive subjects)	P-value
PCV (%)	35.88 ± 6.84	33.49 ± 9.27	0.126
WBC (cells/mm³)	7064.40 ± 2885.75	18354.00 ± 23783.14	0.001
Neutrophils (%)	62.82 ± 15.05	62.82 ± 15.05	0.918
Lymphocytes (%)	36.34 ± 14.78	32.00 ± 14.30	0.119
Eosinophil (%)	1.14 ± .38	2.47 ± 1.53	0.030
Monocytes (%)	1.58 ± 0.52	9.02 ± 14.30	0.097
Platelets (cell/l)	211967.74 ± 70842.31	157741.18 ± 99022.16	0.009
MCH (pg)	33.63±1.58	34.405 ± 6.32	0.961
MCHC (g/l)	337.47 ± 0.00	345.12 ± 28.77	0.403
MCV (fl)	83.81±8.08	100.1 ± 3.05	0.332
HB	13.47±1.11	12.4 ± 4.02	0.074
Basophils (%)	0.40±0.49	0.9.00 ± 0.54	0.11

P<0.05 considered significant

Table 3. Comparison between the haematological indices based on the age of the subject

Variable	< 20 years (41.1%)	20 years and above (58.9%)	P-Value
PCV (%)	31.23 ± 9.55	35.00 ± 8.91	0.141
WBC(cells/mm3)	13923.48 ± 12677.24	21538.44 ± 29089.84	0.245
Neutrophils (%)	60.09 ± 16.11	64.28 ± 14.07	0.310
Lymphocytes (%)	34.65 ± 15.63	30.10 ± 13.19	0.247
Eosinophil (%)	2.64 ± 1.34	2.31 ± 1.70	0.563
Monocytes (%)	12.00 ± 21.11	6.73 ± 4.30	0.220
Platelets (cell/l)	157940.0 ± 106893.63	157612.9 ± 95423.50	0.991
MCH (pg)	37.88 ± 18.96	32.47 ± 11.97	0.263
MCHC (g/l)	356.50 ± 39.15	338.12 ± 17.42	0.043
MCV (f/l)	127.53 ± 204.40	84.57 ± 13.85	0.270
HB	10.74 ± 3.03	11.38 ± 3.37	0.510
Basophils	1.13 ± 0.35	1.13 ± 0.35	1.000

P<0.05 considered significant

Table 4. Comparison between the haematological indices based on gender

Variable	Male (44)	Female (12)	P-value
PCV (%)	33.44 ± 9.99	33.67 ± 6.42	0.942
WBC (cells/mm3)	17912.33 ± 22086.55	19936.67 ± 30177.842	0.797
Neutrophils(%)	62.35 ± 13.89	63.17 ± 19.03	0.869
Lymphocytes (%)	32.91 ± 13.92	28.75 ± 15.80	0.378
Eosinophil (%)	2.00 ± 0.85	4.00 ± 2.24	0.001
Monocytes (%)	6.92 ± 3.90	16.60 ± 29.77	0.058
Platelets (cell/l)	146661.54 ± 89454.18	193750.00 ± 122787.42	0.152
MCH (pg)	35.55 ± 16.28	29.53 ± 2.76	0.307
MCHC (g/l)	346.55 ± 32.07	339.90 ± 9.400	0.545
MCV(f/l)	105.45 ± 139.66	82.31 ± 17.74	0.607
HB	11.11 ± 3.41	11.17 ± 2.40	0.960
Basophils	1.08 ± 0.28	1.33 ± 0.58	0.255

P<0.05 considered significant

Table 5. Comparison of haematological indices based on mortality (deaths) and discharge

Parameter	Discharge (26)	Death (30)	P-value
PVC (%)	36.08 ± 8.66	32.93 ± 10.45	0.230
WBC (cells/mm3)	10814.58 ± 9455.71	25306 ± 46570.01	0.140
Neutrophils (%)	51.21 ± 16.63	67.30 ± 10.863	0.000
Lymphocytes (%)	41.88 ± 14.72	25.60 ± 9.57	0.000
Eosinophil (%)	2.94 ± 1.84	24.88 ± 12.14	0.000
Monocytes(%)	7.29 ± 2.24	6.61 ± 3.95	0.494
Platelets (cell/l)	207272.73 ± 105211.89	121806.90 ± 58219.866	0.001
MCH (pg)	35.33 ± 18.49	33.558 ± 11.3178	0.696
MCHC (g/l)	341.40 ± 9.84	346.77 ± 35.87	0.540
MCV (f/l)	78.53 ± 18.92	86.17 ± 14.06	0.132
HB	11.34 ± 2.94	16.04 ± 26.02	0.441
Basophils	1.00 ± 0.00	1.13 ± 0.354	0.369

P<0.05 considered significant

On the contrary, the levels of total white blood cell, eosinophil and MCH were significantly higher ($p < .05$) in positive cases when compared to the control group. This could possibly be associated to infections, allergy autoimmune diseases or other undetermined underlying illnesses. Furthermore, the platelet level was significantly decreased ($p < .05$) in yellow fever patients when compared to the control group. Interestingly, our result is in line with several reports revealing thrombocytopenia in yellow fever patients. In a very recent report by Neto et al. [20] on assessing some haematological parameters of yellow fever patients, macro, giant platelets and thrombocytopenia was among the observed derangements suggesting bone marrow response to peripheral destruction or consumption of platelets. Also, Crochemore et al. [17] reported reduced level of platelets in a study titled, Thromboelastometry identifies coagulopathy associated with liver failure and disseminated intravascular coagulation caused by yellow fever, guiding specific hemostatic therapy; a case study. They further postulated that platelet consumption, decreased synthesis of clotting factors due to liver damage and disseminated intravascular coagulation are the main causes of severe bleeding and diathesis which is one of the hallmarks of yellow fever infection. Nonetheless, there have been limited reports on the haematological manifestation of these patients.

In this study, 41.1% of the study group were less than twenty (20) years. This aroused the curiosity of the researchers to explore the comparison of the haematological parameters of the study group based on age (Table 3). As shown in table 2 representing comparison of mean levels of packed cell volume, total white blood cell count, neutrophil, lymphocyte, eosinophil, monocyte, platelet, MCH, MCHC, MCV, HB and basophil based on the age of positive patients. There was no significant difference ($p > .05$) in the aforementioned indices between subjects below 20years and their counterparts above 20years except MCHC which was significantly lower ($p < .05$) in positive subjects over 20 years. This unvariedness in the assayed haematological parameters under comparison could be alluded to the fact that about 96.4% of the test subjects were below 50 years of age hence, fall under the same reference values for the haematological indices under review. On the other hand, the significantly lower value of MCHC may be associated with diet and alterations in iron

metabolism which occurs as a result of viral infection.

Table 4 showed comparison of mean levels of the haematological indices based on the gender of positive patients. The level of eosinophil was significantly higher ($p < .05$) in females when compared to male subjects. This finding is in keeping with earlier reports such as that of Klein et al. [21] who submitted that females develop more frequent reactions and responses to allergic episodes and inflammation arising from exposure to viral antigens. It is worthy to note that the result of this study revealed a higher incidence of yellow fever in males than in their female counterparts where 44 out of the 56 yellow fever positive patients admitted in the Centre were males with only 12 females. According to Furman et al. [22], females demonstrate greater antibody responses than males. Also, it has been reported that a large number of immune-related genes encoding proteins, including IL-2 receptor- γ chain, IL-3 receptor- α chain, IL-13 receptor- α chain, GATA1, CD40 ligand, TLR7 and TLR8 are located on the X chromosome. This implies that X-linked genes are determinants of immunocompetence. Hence, females with XX (double the number of X) chromosomes would demonstrate better immune competence than their XY male counterparts [23].

Table 5 showed comparison of mean levels of the haematological indices based on survival and mortality. The levels of neutrophils and eosinophils were significantly higher ($p < .05$) in deceased subjects when compared to discharged positive subjects whereas the lymphocyte and platelet levels were significantly lower ($p < .05$) in deceased subjects when compared with their positive subjects who were discharged. Elevated neutrophil and eosinophil levels could be attributed to infection, allergy and inflammation associated with the infection. Furthermore, significantly lower level of platelet observed in the deceased patients could possibly be due to liver dysfunction seen in these patients as it is the primary organ of viral invasion. Infiltration of the liver by yellow fever virus results to distortion of the liver cells leading to decreased synthesis of clotting factors including platelets which culminates in disseminated intravascular coagulation, one of the major causes of mortality in yellow fever patients.

Additionally, although our study could not establish correlation between haematological

indices and mortality due to insufficient data, researchers have explored possible correlation of some variables including haematological indices to mortality. Recent research by Kallas et al. [19], titled: Predictors of mortality in patients with yellow fever: an observational cohort study revealed that different markers are associated with death including age, sex, leukocyte and neutrophil counts, liver transaminase concentration, International Normalized Ratio (INR), bilirubin concentration, creatinine concentration, and yellow fever viral load. They further elucidated four different factors that can influence the outcome of human yellow fever virus infection. According to their submission, the first factor is increasing age, possibly reflecting immune system senescence or diminished functional reserve, in line with the findings of a previous study assessing patients with yellow fever in Ghana and Nigeria [24]. Furthermore, similar observations were made in patients with dengue in Singapore [25]. They outlined the second factor as higher numbers of circulating neutrophils which might reflect increased inflammation due to a cytokine storm, sepsis, or bacterial product translocation. The third factor pointed out was elevated AST known to be a proxy for liver damage as well as multiorgan failure. The fourth possible factor that could affect the outcome of yellow fever infection as revealed by their study is the pathogen itself. They opined that even though viral load has not been previously identified as a predictor of death in human beings, they were able to document this association, supporting the idea that there is a direct viral effect on disease pathogenesis.

It is important to recognize that in the general management of yellow fever infection, the monitoring of laboratory indices including haematological and haemostatic indices will give an insight towards disease progression and predicting outcome.

4. CONCLUSION

In this study, we observed higher levels of total white blood cell, eosinophil and MCH and lower levels of platelet in hospitalized yellow fever subjects. Other haematological indices assessed appeared normal. Lower level of MCHC was seen in yellow fever subjects above 20 years of age while there was no difference in other haematological parameters based on age. However, there is a significant difference in eosinophil level based on gender. The levels of neutrophils and eosinophils were significantly

higher in deceased subjects whereas the lymphocyte and platelet levels were significantly lower in deceased subjects when compared with their positive subjects who were discharged. Understanding these characteristics aids in the management and prognosis of patients as well as monitoring their outcome. We therefore recommend further research in this area as this will give better insight in this regard.

CONSENT

Both oral and written consent was obtained from each yellow fever patient and the control subjects before their recruitment into the study.

ETHICAL APPROVAL

Ethical approval was sought and obtained from the Research and Ethics Committee of the Federal Medical Centre (FMC) Asaba, Delta State, where the participants were recruited from. The approval letter from this committee has the following reference number:

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interests between the authors and the producers of the products because we do not intend to use these products for the purpose of litigation, but for the advancement of knowledge. Also, the research was not funded by the producing company but by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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