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Review Article

Stevens - Johnson Syndrome and Toxic Epidermal Necrolysis; Extensive Review of Reports of Drug-Induced Etiologies, and Possible Therapeutic Modalities

Adegbenro Omotuyi John Fakoya*, Princess Omenyi, Precious Anthony, Favour Anthony, Precious Etti, David Adeiza Otohinoyi, Esther Olunu

All Saints University, School of Medicine, Roseau, Dominica

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***Correspondence:** Adegbenro Omotuyi John Fakoya. All Saints University, School of Medicine, Roseau, Dominica. E-mail: gbenrofakoya@gmail.com

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Abstract

Stevens - Johnson Syndrome and Toxic Epidermal Necrolysis are adverse hypersensitivity reactions that affect the skin and mucous membranes. They are characterised by erythematous macules and hemorrhagic erosions of the mucous membranes. Epidermal detachments of varying degrees of severity also occur in these conditions. Various aetiologies are associated with these conditions, with adverse drug reaction being the most common. Though the worldwide incidence of these conditions is recorded as low, diverse types of medication are being observed to lead to these conditions. This review compiles information on the details of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis, the pathophysiology, therapeutic management, and largely considers the drug-induced etiologies associated with these conditions.

Introduction

Stevens-Johnson syndrome (SJS) is a dermatological condition with the more severe form being toxic epidermal necrolysis syndrome (TEN) or Lyell's syndrome. These two syndromes are said to exist at the two ends of the spectrum of an adverse skin reaction occurring from severe epidermolysis [1]. They present as severe exfoliative reactions affecting mainly the skin and mucous membranes [1]. The characteristic clinical presentation includes mucocutaneous tenderness, hemorrhagic erosions, and erosion of the mucous membrane, erythematous macules, blisters and denuded skin occurring as a result of the severe separation of the epidermis from the dermis [2]. The Bastuji-Garin et al. criterium is used in the diagnosis of SJS/TEN in which patients are classified into three categories based on the degrees of skin detachment [2], while the international classification uses the affected body surface area (BSA); SJS involves lower than 10% of the BSA, while TEN affects greater than 30% of the BSA. The definition of SJS and TEN incorporates an overlap which shall be highlighted in Table 1 below. It has been shown that SJS and TEN have mortalities in the range of 10 to 50 percent [3].

SJS/TEN can present in any age group but occurs more frequently in women, HIV-Infected patients, and the elderly. The global incidence rate associated with TEN is low, estimated in 2005 between 0.4 and 1.2 or 1.3 per million persons yearly. An epidemiologic study of TEN in France gave a similar incidence of 1 to 1.3 cases/million/ annum [4].

However, as the years' advance, the numbers of incidence seem to be increasing in other parts of the world. Literature shows a correlation between the incidence and increasing age. The incidence increases sharply with increasing age, as does the use of drugs with ageing [5]. Females are most commonly affected represented by a female-male ratio of 3:2. The average age of patients reported is between the ages of 46 and 63, while the proportion of females is estimated between 61.3% and 64.3%, respectively [4]. Reports have also been linked to patients with Human Immunodeficiency Virus (HIV)-1 infection, recipients of bone-marrow transplants and systemic lupus erythematosus (SLE) [5].

Drug hypersensitivity has been associated with relatively complex genetic factors, which have been studied in diverse populations as well as in a variety of ethnic background. Chung et al., demonstrated a uniquely strong correlation between drug hypersensitivity (Carbamazepine triggered SJS), ethnic background (Hans Chinese) and Human Leucocyte Antigen (HLA)-B*1502 [3]. This strong association resulted in a further investigation into a similar cohort of Hong Kong Han Chinese having severe adverse cutaneous reactions to anticonvulsant drugs [6].

In another study of a Thai population, the susceptibility of individuals with HLA-B*1502 to the anticonvulsant carbamazepine was confirmed [7]. However, a weak association between carbamazepine and HLA-B*1502 was only demonstrable in an Indian-based study. While no genetic correlation could be established in Europeans and Japanese [8][9].

To further corroborate this non-genetic association in Europeans, a large study (RegiSCAR) carried out an HLA-B genotype on patients who suffered severe adverse cutaneous reactions triggered carbamazepine, lamotrigine, sulfamethoxazole, allopurinol, and NSAIDs of oxicam-type regarded as high-risk drugs. The study showed that HLA-B*1502 is not a confirmatory marker for any of the studied high-risk drugs known to cause SJS/TEN, and hence cannot be authoritatively labelled the cause of pathology in Europeans [10][11]. Therefore, it can be concluded that for SJS/TEN in individuals exposed to Carbamazepine, "the genetic constellation of HLA-B*1502 is not a population independent marker" [6].

HLA-B*5801 is another genotype which has been highly correlated with SJS/TEN in Han Chinese patients exposed to allopurinol. The study showed a 100% correlation of allopurinol exposure to HLA - B*5801 positive genotype in patients who presented with the adverse drug reactions [12]. Subsequent studies further revealed a high correlation between HLA-B*5801 and SJS/TEN in Thai patients [7], Japanese patients [9], and too much lower degree patients of European descent (about 55% of cases) [11].

Epidermal necrosis that occurs as a part of the TEN disease process is mainly associated with massive keratinocyte apoptosis [4]. This is mediated by surface receptors such as tumour necrosis factor (TNF) receptor (Fas), and when coupled with the Fas ligand causes disassembly of DNA and cell death by the induction of apoptosis [7]. Cell death could also be modulated by death receptor-independent mechanisms that include the release granzyme-B and perforins from cytotoxic T lymphocytes, thus activating the caspase-dependent or caspase-independent mechanism [12].

Clinical Presentation

The initial presentation of SJS/TEN may include non-specific symptoms such as fever, discomfort with swallowing, and stinging eyes. Typically, the cutaneous manifestations of SJS/TEN are usually preceded by these non-specific symptoms [13] [14]. Early locations for skin involvement include the presternal truncal region, the face, and could also involve the palms and the soles. In about 90% of patients, there is involvement of the mucosa of the mouth, genital and/or gastrointestinal tracts visible as erythema and erosions [13] [14]. Other frequent presentations at the beginning of the pathology is eye related and this ranges from acute conjunctivitis, erythema, edema of the eyelid, ocular discharge and crusting, to corneal erosion, the formation of conjunctival membrane or pseudomembrane, and in severe cases, to corneal ulcerations, cicatrizing lesions, fornix shortening, and symblepharon [15] [16]. However, late complications of SJS/TEN cannot be predicted by the severity of acute ocular manifestations [17]. Erythematous and livid macules typify the morphology of early cutaneous lesions.

Table 1: Clinical manifestations distinguishing SJS, SJS-TEN overlap, and TEN [2]

Clinical entity	SJS	SJS-TEN overlap	TEN
Primary Lesions	Dusky red lesions Flat atypical targets	Dusky red lesions Flat atypical targets	Poorly delineated erythematous plaques Epidermal detachment Dusky red lesions Flat atypical targets
Distribution	Isolated lesions Confluence (+) on face and trunk	Isolated lesions Confluence (++) on face and trunk	Isolated lesions (rare) Confluence (+++) on face, trunk, and elsewhere
Mucosal involvement	Yes	Yes	Yes
Systemic symptoms	Usually	Always	Always
Detachment (%body surface area)	< 10	10-30	> 30

The second phase is characterised by the development of wide-spread areas of epidermal separation. If no epidermal separation is observed, it warrants more detailed skin examination during which a tangential mechanical pressure is exerted on many erythematous areas, called Nikolsky sign. If the

mechanical pressure causes and epidermal detachment, Nikolsky sign is positive. However, Nikolsky sign is not only defined for SJS or TEN, as it can equally be positive in conditions like the autoimmune bullous cutaneous pathologies like the pemphigus vulgaris [15] which can be utilised as a distinguishing feature from a similar autoimmune condition, bullous pemphigoid.

A major prognostic factor is the degree of cutaneous involvement. The evaluation of the degree of skin involvement should only include the already detached necrotic skin or detachable skin, that is, those that are Nikolsky positive [17].

Magina and colleagues [16] reported the following presentations for the late phase of TEN: Cutaneous hypo and hyperpigmentation (62.5%), nail dystrophies (37.5%), and the rest being eye complications. In another study, Yip et al. reported late ocular complications in about 50% of patients with TEN and reported them by ranking them in decreasing frequencies; “severe ocular dryness (46% of cases), trichiasis (16%), symblepharon (14%), distichiasis (14%), visual loss (5%), entropion (5%), ankyloblepharon (2%), lagophthalmos (2%), and corneal ulceration (2%)” [18]. Hypertrophic scars have only been reported in a handful of patients [19]. Reports have shown that 73% of patients with acute phase mucosal involvement subsequently presented with long-term complications with mucosal sequelae involving the oral and oesophagal mucosa majorly, and to a lesser degree, the genital and pulmonary mucosa [20]. Similarly, a nine-patient SJS/TEN study showed seven of the patients presenting with either keratoconjunctivitis or xerostomia or both, with a resemblance to Sjogren-like syndrome [21]. Furthermore, another report revealed a patient with “Sjögren-like pluriglandular exocrine insufficiency”, which is also resulted in an impairment of the exocrine pancreas [22].

Drug etiologies associated with SJS and TEN

A major percentage of the disease is caused by medications, while the remaining is due to upper respiratory infections such as HIV [23], Hepatitis virus, Herpes virus, Mycoplasma pneumoniae [24] [25]. Others include malignancies, as well as idiopathic. A substantial number of medications have been implicated in the aetiology of SJS/TEN. This article has attempted to review as many as possible of the published reports. The table 2 below summarises some drug categories that have been implicated in the aetiology of SJS/TEN.

Table 2: Reported cases of drug-induced sjs/ten

Drug Classification	References
Antibiotics	23-34
Anticonvulsants	35-41
Sulfonylureas	42
Diuretics	43-44
Analgesics	45-48
Antidepressants	49-50
Tyrosine Kinase Inhibitors	51-54
Xanthine Oxidase Inhibitors	55
Androgenic hormones	56-57
Antineoplastic drugs	58-60
Antiviral drugs	61-63
Combination drug(Aggrenox)	64
Immunosuppressant/modulators	65-67
Antihistamines	68
Angiotensin-converting enzyme inhibitors	69
Anti-osteoporotic agent	70
Contrast agent	71
Insecticide	72-73

Antibiotics

Sulfonamides: Among the antibiotics, the most implicated high-risk cause of SJS/TEN are the sulfonamides especially *Trimethoprim - Sulfamethoxazole* which accounts for about 69% of cases. The other non-sulfonamide antibiotics are considered low risk [23] [24]. Figure 1, is a female patient with adverse cutaneous reaction from Trimethoprim-Sulfamethoxazole prescribed for an upper respiratory tract infection.

Figure 1: Patient with SJS/TEN caused by Trimethoprim - Sulfamethoxazole, before the commencement of therapy

Aminopenicillins: Aminopenicillins have been shown to be the most frequent causes of SJS when compared to the other antibiotics. This could be due to how frequently they are prescribed [25]. *Amoxicillin/clavulanic* acid (Co-amoxiclav) even resulted in SJS in an 18-month-old child treated post-caustic poisoning and esophagogastric necrosis [26].

Fluoroquinolones: Ciprofloxacin induced SJS in a patient treated for otitis media reported in Sweden. [27] *Norfloxacin* induced SJS may appear similar to pemphigus, hence making early diagnosis a bit difficult [28].

Tetracyclines: Doxycycline has been implicated in the aetiology of SJS in the systemic use of ophthalmologic eyelid and ocular surface disorders [29]. *Minocycline* has been shown to induce both SJS and concurrent bilateral Parotitis in a young boy [30].

Macrolides: Azithromycin has been shown to cause SJS after a five-day outpatient completion [31].

Cephalosporins: Cefotaxime has been implicated in causing SJS when administered to an elderly lady for treatment of upper urinary infection [32], likewise *Cefepime* [33].

Metronidazole: Metronidazole induced SJS tends to start off with neurological manifestations before mucocutaneous and skin eruptions. This is worth noting, as patients should be advised of the early symptoms to prevent this rare adverse effect [34].

Anticonvulsants

Phenytoin: There is a possible association between the HLA-B*1502 allele and phenytoin-induced SJS in Asian patients. This is still under review by the FDA. This could mean a possible genetic predisposition to getting SJS in certain populations as opposed to others [35].

Lamotrigine: A potential rare side effect of SJS/TEN has been implicated regardless of appropriate dosing and adjustments; Concurrent use with Valproic acid increases risk [36].

Carbamazepine: Increased frequency of its use for pain control has further increased its implication in causing SJS/TEN [37].

Oxcarbazepine: A case was reported in India after use for treatment of epilepsy in a 21 – year-old male. SJS occurred 2 weeks during treatment despite accurate titrations [38].

Phenobarbital: Risk increases within the first 2 months of treatment. Genetic predisposition has been associated with this medication in conjunction with SJS/TEN [39].

Sodium valproate: A potential cause of SJS/TEN, though lower risk than the rest of the anticonvulsants. Increased risk when used together with other anticonvulsants. When used as monotherapy, it rarely causes SJS. However, if it occurs, it seems to be restricted to the involvement of only the oral mucosa [40].

Levetiracetam: It has been implicated in hypersensitivity syndrome reactions as well as SJS. Although rare it can be probably dose related [41].

Sulfonylureas

Glipizide: A study showed the increase in dosage from 5mg to 10 mg in a certain patient triggered a complex immune reaction that resulted in SJS the following day, it was postulated it could be due to the certain delayed immune reaction and possibly due to hapten hypothesis [42].

Diuretics

Furosemide: A potential adverse effect is SJS, especially when used as an additive with other sulfa-containing drugs [43].

Acetazolamide: A commonly used drug in ophthalmology. It is also a sulfonamide as well as a carbonic anhydrase inhibitor. It's been associated with fatal SJS in patients of Korean and Japanese descents. HLA-B59, which is specific to Japanese descents, is a risk factor [44].

Analgesics

i) Non-steroidal anti-inflammatory drugs (NSAIDS):

Diclofenac: It could cause SJS especially in the elderly; caution should be applied when prescribing this drug [45].

Ibuprofen: SJS occurred in a Nepali male after taking 400mg of Ibuprofen every 8 hours for 2days. It could be due to genetic predisposition by HLA type or some inflammatory mediators causing epithelial damage [46].

Rofecoxib: A selective COX-2 inhibitor that has decreased gastrointestinal side effects was shown to cause SJS after three weeks of administration to a patient with systemic arthralgia [47].

ii) Paracetamol (Acetaminophen):

Paracetamol was shown to cause SJS/TEN despite its fair safety margin. It was shown to be dose-dependent in causing SJS [48].

Antidepressants

Mirtazapine: A patient with Systemic lupus erythematosus (SLE) who took mirtazapine for depression presented with SJS after 15 days of use. Though a very rare cause of SJS. The presence of the autoimmune disease led to a dilemma between either SLE or mirtazapine as the cause. The history and resolution of the disease eventually pointed to Mirtazapine as the culprit [49].

Duloxetine: The study showed 0.01% of patients treated with this medication could potentially cause SJS. An adolescent was affected in this study; so far it had only been adults involved [50].

Tyrosine kinase inhibitors

Afatinib: SJS can be seen in patients treated with Afatinib for Non-small cell lung cancer (NSCLC) [51].

Vandetanib: Also used in the treatment of NSCLC, was shown to cause SJS in certain patients

[52].

Imatinib: SJS occurred in a patient treated with Imatinib for chronic myeloid leukaemia after treatment for 2 days. Caution should be taken in the prescription of this medication, as SJS is a potential adverse effect [53].

Sunitinib: A patient was treated with Sunitib for renal cell carcinoma with metastasis to the lung. On day 14 of treatment, the patient presented with SJS [54].

Xanthine oxidase inhibitor

Allopurinol: Commonly used in the treatment of chronic gout. It is usually considered a safe drug, and due to its frequent administration, increased risk for SJS/TEN is possible, also common in genetically predisposed patients especially in the Han Chinese population [55].

Androgenic hormones

Danazol: A patient diagnosed with systemic lupus erythematosus was prescribed danazol for treatment of autoimmune hemolytic anaemia. It has been approved as a second line agent in SLE related haematological disorders including thrombocytopenia [56].

Androgenic anabolic steroids: An athlete involved in the illicit use of steroids presented with SJS immediately after injecting drostanolone propionate, danazol, and metenolone enanthate [57]. Considering the common use of steroids for body performance, patients should be alerted to this rare side effect.

Antineoplastic drugs

Paclitaxel: An antineoplastic agent used to treat several cancers; Though SJS could be a rare complication, caution is advised when prescribed. A 53 – year-old male treated with Paclitaxel manifested symptoms after administration of second dose [58].

Docetaxel: Due to its strong toxicity, a patient presented with SJS after its use as a chemotherapeutic agent. Skin eruptions erupted after the first cycle of chemotherapy [59].

Tegafur/gimeracil/uracil (TS-1): A 78-year-old Japanese male presented with SJS eight days after treatment for carcinoma of the oral floor. Further tests showed an association between drug eruptions and antinuclear antibodies and positive drug-induced lymphocyte stimulation test [DLST] [60].

Anti viral drugs

i) Neuraminidase inhibitor (Oseltamivir); the medication is popularly known as Tamiflu and is indicated for prevention and treatment of Influenza. Considering the increased use of this drug, there are concerns about an increased risk for SJS [61].

ii) Nucleoside reverse transcriptase inhibitor (Adefovir): Commonly used in the treatment of Hepatitis B and Herpes simplex virus. A case of SJS was reported due to adefovir use [62].

iii) Non-nucleoside reverse transcriptase inhibitor (Nevirapine): Commonly used in the combination treatment for HIV. Patients infected with HIV-1 are more prone to SJS [63]. Figure 2 shows a healing adverse cutaneous reaction from Nevirapine (a component of the HAART) for a patient diagnosed with HIV.

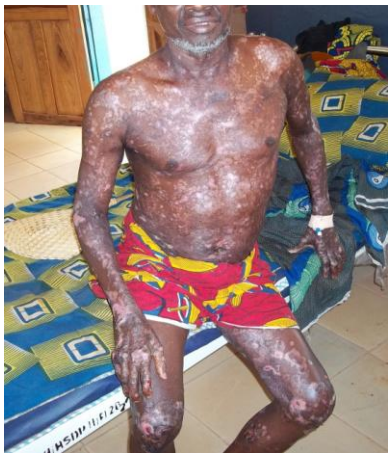

Figure 2: Patient with SJS/TEN caused by Nevirapine responding to therapy

Aggrenox

This is a combination of Aspirin and Dipyridamole, it is mainly used for stroke reduction in high-risk patients. It caused SJS in an elderly Chinese woman with transient ischemic attack who was recently switched from aspirin to Aggrenox [64].

Immunosuppressants/immunomodulators

i) Immuno-modulatory imide drugs (IMiDs):

Thalidomide: This is approved for use in the treatment of multiple myeloma. It inhibits Interleukin 6 (IL-6), a vital component in the proliferation of myeloma cells. A study once showed thalidomide could be used to treat SJS/TENS. However a case of SJS was reported with its use. This contradiction is worth noting [65].

Lenalidomide: Though similar to thalidomide, it has shown to have lesser adverse effects. A rare adverse effect is SJS [66].

ii) Imidazole nucleoside:

Mizoribine: An immunosuppressant used in

renal transplants, lupus nephritis and rheumatoid arthritis. A 32-year-old Japanese woman diagnosed with SLE was started on mizoribine for lupus nephritis. She desired pregnancy hence cyclophosphamide was not used. Mizoribine induced SJS 6 months later despite its known safety margin [67].

Antihistamines

Fexofenadine: Telfast-D a drug containing both fexofenadine-pseudoephedrine was prescribed to a patient due to unrelenting allergic rhinitis. It further resulted in SJS. It was confirmed by skin testing (prick, intradermal and patch) which showed a positive reaction 96 hours later [68].

Angiotensin-converting enzyme inhibitors

Ramipril: Ramipril resulted in SJS after being newly prescribed for a patient for hypertension. ACE inhibitors are known to interfere directly with cell cohesion causing bullous eruptions, which are similar to pemphigus vulgaris or bullous pemphigoid. These reactions are usually non-immunological [69].

Antiosteoporotic agent

Strontium ranelate: It is known as a dual action bone agent (DABA) because of increases deposition of bone by osteoblasts and decreases resorption of bone by osteoclasts. A 67-year-old Chinese woman was diagnosed with SJS 3 weeks after starting this medication for treatment of post-menopausal osteoporosis [70].

Other reported non-therapeutic agents/chemicals in the aetiology of SJS

Iopentol: This is a contrast medium. A 6year old diagnosed with Hodgkin's disease was injected with iopentol to undergo CT scan to explore his lymphadenopathy. Three days later he presented with SJS [71]. Knowing how common CT scans are used, it is worth noting the potential adverse effect of contrast medium.

Carbamate: This is an insecticide. A 63 – year-old farmer was exposed to the insecticide two days before presenting with SJS. He wasn't on any medication. He admitted to contact of the carbamate with his skin [72]. There has been a reported case of TENS associated with oral ingestion of carbamate as a suicide attempt [73].

The therapeutic approach to SJS and TENS

The treatment modality employed in patient management is dependent on the aetiology of the disease which as previously mentioned could be; infectious, drug-induced, as well as malignancies or idiopathic [74].

The first step to the treatment of SJS and TENS is to eliminate the causative factor. In cases of SJS/TENS caused by infections with organisms, the patient is treated with the appropriate antimicrobial. For drug-induced SJS/TENS, the offending drug is withdrawn immediately [75].

The next step is the provision of supportive care for the patient. This includes administration of intravenous fluids as well as parenteral or nasogastric feeding. Patients are also to be kept in a warm environment [76].

The final step is symptomatic treatment. Several methods have been employed in symptomatic treatment (Table 3**).**

Table 3: Various approaches in the management of SJS and TEN

Therapy	Mechanism of Action	Advantages	Disadvantages	Reference
Systemic Corticosteroids	They decrease immune response to an exogenous agent.	Since SJS/TEN is thought to be as a result of an immune response of the body to an exogenous agent, corticosteroids may decrease the severity of this response.	Corticosteroids are possible causative factors for SJS/TENS. Some studies show that they can increase the risk of infections.	[77, 78]
Human Intravenous Immune Globulin (IVIG)	In addition to a combination of immunoglobulins, IVIG contains autoantibodies against Fas receptors. Fas receptors are on the surface of keratinocytes. When bound to by the Fas ligand they mediate the Fas-Fas ligand-mediated apoptosis. The autoantibodies in IVIG bind to Fas receptors to prevent this apoptotic process	Autoantibodies in IVIG are believed to reduce complications of TEN. It can be used in combination with corticosteroids as management therapy resulting in a better chance of decreasing mortality rate. It was discovered that when compared to supportive care only, early intervention with IVIG appeared to significantly improve the ocular involvement of SJS/TEN.	Some studies record higher mortality rates with the use of IVIG when compared to supportive care or corticosteroids	[77, 78]
Cyclosporine	It inhibits calcineurin and thus decreases T cell activity. It acts as an immunosuppressant. It can also prevent the process of apoptosis through the downregulation of NF-kB.	Patients treated with cyclosporine completed re-epithelization more quickly than with other treatments. Fewer numbers of patients treated developed organ failure and died than with other treatments.	Leukoencephalopathy, neutropenia, pneumonia, and nephropathy.	[77, 79, 80]
Plasmapheresis	This process involves the filtration the patient's blood. -The cellular component is separated, and the plasma is discarded. -Artificial plasma and albumin is added to the filtered cellular components and then re-transfused back into the patient. -This is done to eliminate the non-dialyzable pathogens in the plasma.	- It is a safe procedure. -it has yielded favourable results with survival rates of 77-100% after 1 to 8 exchanges.		[78]
Granulocyte Colony Stimulating Factor	-It increases neutrophil counts.	-It can reduce the risk of infection in neutropenic patients with SJS/TEN.		[77]

Other potential therapeutic measures like the TNF-alpha inhibitor, thalidomide and

Cyclophosphamide have been associated with increased mortality [77].

In conclusion, SJS and TEN are both life threatening adverse hypersensitivity reactions. Proper understanding of the etiology as well as the progression of these conditions is necessary for early diagnosis as well as treatment. It is expected that the investigation of the mechanism of action of drugs associated with SJS and TEN will improve the current understanding of the condition with aim of eliminating its incidence. There are existing treatment modalities for these conditions, however, there is no therapeutic measure defined as superior to others. It has however been observed that the earlier these conditions are diagnosed and managed the better the prognosis.

Authors Contribution

AOJ, PO, PA, FA, PE, DO and EO wrote the manuscript; AOJ and DO reviewed the manuscript; all the authors approved the manuscript for publication.

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