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Table of Contents

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Factors Associated to Cataract Surgery Failure at Kankan Regional Hospital

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Abstract

Introduction: Cataract surgery has undergone many changes with the size of incision progressively decreasing over time with an incision of 12.0 mm for intracapsular cataract extraction to 2.2 - 2.8 mm in phacoemulsification. However, phacoemulsification due to high cost and equipment maintenance cannot be employed widely in developing countries. The phacoalternative or Manual small-incision cataract surgery (MSICS) offers similar advantages with the merits of wider applicability, less time consuming, a shorter learning curve, and lower cost. Haven't not being without complications like any other surgery We have identified the factors influencing the outcome of phacoalternative cataract surgery in order to improve our quality of care for our patients suffering from blindness induced by the world's first leading cause of legal blindness. We have identified the factors influencing the outcome of cataract surgery. **Patients and Methods:** This was a prospective observational study of the descriptive type lasting six (6) months from March 1 to August 30, 2020 including all patients operated on for cataracts and having lower visual acuity at 3/10. The operating form included demographic data, the patient's personal ophthalmological history, postoperative visual acuity, per and postoperative complications and the type of pathology involved. The analysis was carried out using epi-info 7.2.0.1 software. **Results:** During this study period, we collected 61 cases of failure of cataract surgery out of a total of 1182 operated eyes, *i.e.* a frequency of 5.16%. Women represented more than half of the sample with 74%. Almost all of our patients, *i.e.* 96.72%, were over the age of 60. Loss of visual acuity was the main complaint in all our patients, *i.e.* 100% followed by photophobia with 24.4% of cases. Arterial hypertension present in 8.20% of patients was the most common comorbidity in our series followed by diabetes with 4.92%. 18 patients (29.5%) presented early post-

operative complications such as corneal edema in 15 patients (24.6%) and hyphema in 3 patients (4.9%). Late postoperative complications were dominated by capsular fibrosis encountered in 42.89% of our patients. The causes of failure after cataract surgery were dominated by selection errors which accounted for 36.06% followed by late postoperative complications 34.43%. **Conclusion:** Like any surgery, cataract surgery can often be marred by various complications often occurring during the intraoperative or postoperative period. These complications in addition to negligence and/or non-deep analysis of certain cases (selection) are often associated with poor functional recovery.

Keywords

Cataract, Small Incision, Complications, Failure

1. Introduction

Cataract is the partial or total clouding of the lens [1]. It is the leading cause of curable blindness in the world and accounts for 50% of all causes of blindness [2].

The treatment of cataracts is surgical, several techniques exist whose reference is phacoemulsification. However, its practice is not widespread in developing countries because of the cost of phaco-alternative or small-incision cataract surgery.

Small Incision for Cataract Surgery (SICS) gives results comparable to phacoemulsification [3]. This operation has benefited from many technological advances, both in terms of surgical technique and implant development. It is performed on an outpatient basis, under simple local anesthesia [1].

However, there are causes of poor visual results at the end of cataract surgery that can be divided into three groups: inadequate correction of postoperative ametropia (lack of glasses), inability to detect pre-existing conditionsocular conditions (poor selection of candidates for surgery) and surgical complications.

The preoperative and postoperative complications of cataract surgery are extreme, unpredictable but some can be disastrous, threatening the visual acuity or even the integrity of the eyeball, hence the interest of taking all precautions to avoid them.

Nowadays, few studies have been done to identify the factors associated with cataract surgery failure. For the most part, they set out to evaluate the results without determining the share attributable to each of the factors involved [4] [5].

This is why we initiated this study which aims to identify the causes of poor results of phacoalternative cataract surgery.

2. Materials and Methods

We conducted a six-month descriptive prospective study on cataract patients during the period from 1st of March to August 30, 2020 at the ophthalmology

department of Kankan Regional Hospital.

All patients operated on cataracts and who had a corrected visual acuity of less than 3/10 on the 60th day postoperative were considered. The exclusion criteria were all patients who were operated cataract surgery by the phacoalternative technique and who had a corrected visual acuity greater than 3/10 on the 60th day postoperatively and all other cases of surgery observed for other diseases and techniques at Kankan Regional Hospital.

For each included case, we collected on a collection sheet, socio-demographic characteristics, ophthalmological and medical history, conditions of surgery, postoperative follow-up, corrected postoperative visual acuity, data from ophthalmological examination and additional examinations in order to identify the cause of the poor postoperative result. These causes were divided into inadequate correction, postoperative complications and poor patient selection.

All our patients were operated on by the same surgeon. They all benefited from a posterior chamber implantation with a rigid polymethylmetacrylate (PMMA) artificial lens whose power was previously calculated with the SRK II formula. Complicated cases of a rupture of the posterior capsule were implanted with iridescent fixation implants.

All patients who met our inclusion criteria and who on the 60th day postoperative by the phacoalternative technique had not obtained at least 3/10th as visual acuity by far with the best correction, patients in whom corneal edema persisted, the presence of secondary cataracts having impacted an improvement in visual acuity were considered surgical failure. Inadequate corrections were for patients who did not receive the implants according to the biometrics previously calculated before the intervention according to the SRK-T formula.

The input and analysis were done using the Epi info 7.2 software.

The confidentiality of the data has been respected according to the standards of ethics and professional conduct.

3. Results

During this study period, we collected 61 cases of cataract surgery failure out of a total of 1182 operated eyes, a frequency of 5.16%.

The implant used corresponded to the power calculated in 50 patients or 82%.

The average age of our patients was 65.04. More than half (68.85%) were in the 60 - 69 age group (**Table 1**).

The female sex was the most represented with a sex ratio of M/F of 0.35.

On the 60th day postoperatively, the most frequent complaints in our patients were the persistence of the decrease in visual acuity (100%) and photophobia (34.4%) (**Table 2**).

High blood pressure (8.20%), diabetes (4.92%) and the notion of trauma (1.64%) were the history found in our patients.

Biomicroscopic signs were dominated by postoperative corneal edema (24.59%), posterior capsule opacification (14.75%) and mydriasis (3.27%) (**Table 3**).

Table 1. Distribution of cataract patients with poor functional recovery from 01 March to 30 August 2020 by age.

Age range	Actual	Percentage
60 - 69 years	42	68.85
70 - 79 years	17	27.87
40 - 49 years	2	3.28
TOTAL	**61**	**100.00**

Table 2. Distribution of cataract patients with poor functional recovery from 1st March to 30th August 2020 according to functional signs.

Complaints	Actual	Percentage
BAV	61	100.0
Photophobia	21	34.4
Myodesopsias	18	29.5
Pain	9	14.8
Visual blurring	8	13.1

Table 3. Distribution of cataract patients with poor functional recovery from March 01 to August 30, 2020 according to biomocroscopic examination.

CA	Actual	Percentage
Narrow CA	1	1.64
Deronde pupil	2	3.27
Corneal edema	15	24.59
Posterior capsule fibrosis	9	14.75
Mydriasis	2	3.28
Myosis	2	3.28

In the posterior segment, non-glaucomatous optic neuropathy was found in 9.83% of cases, glaucomatous optic neuropathy (8.19%) and macular scar (6.55%) (Table 4).

The only intraoperative complication was the rupture of the posterior capsule reported in two patients (n = 2) or 3.27%.

Corneal edema (24.6%) and hyphema (4.91%) were the two early postoperative complications found in our patients.

Late postoperative complications were posterior capsule fibrosis (42.86%), postoperative astigmatism (28.57%), macular edema (28.57%) and corneal decompensation (8.19%) (Table 5).

As the cause of the poor functional result, we blamed postoperative complications in 21 patients or 34.43% of cases, an unsuitable implant 12 patients or 19.67% of cases and selection errors 45.9% of cases (Figure 1).

Table 4. Distribution of cataract patients with poor functional recovery from March 01 to August 30, 2020 according to the pathologies of the posterior segment.

Fundus	Actual	Percentage
Optical atrophy	6	9.83
Glaucomatous papilla	5	8.19
Retinitis pigmentosa	1	1.64
Macular scar	4	6.55
Vitré trouble	3	4.91
AMD	3	4.91

Table 5. Distribution of cataract patients with poor functional recovery from March 01 to August 30, 2020 according to late postoperative complications.

Complications	Actual	Percentage
Post op astigmatism	6	28.57
Posterior capsule fibrosis	9	42.86
Macular edema	6	28.57
Corneal decompensation	5	8.19
Total	**21**	**100.00**

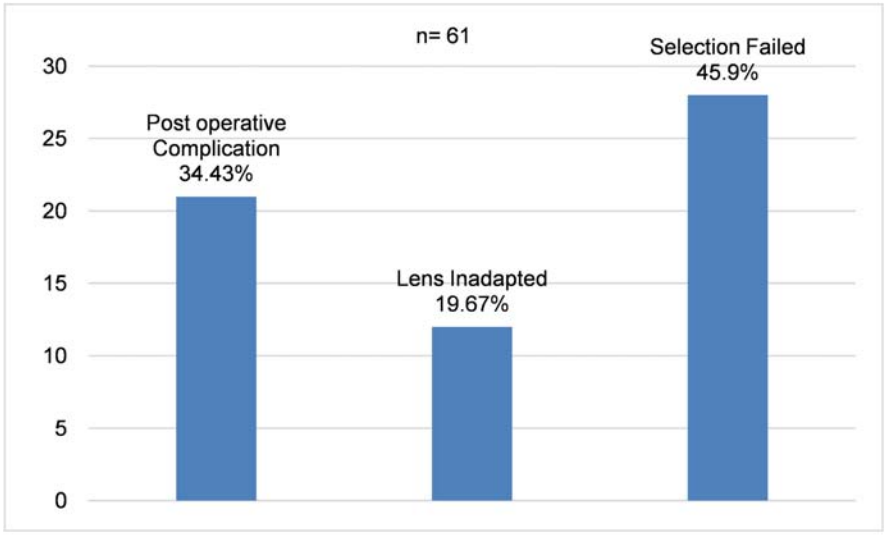

Figure 1. Distribution of cataract patients with poor functional recovery from March 01st to August 30th, 2020 because of the causes.

4. Discussion

From 1st March to August 30th 2020, we conducted a prospective observational study on the causes of failure after cataract surgery. The general objective of this study was to identify the causes of poor outcomes of phacoalternative cataract surgery with posterior chamber implantation.

During this study period, we collected 61 cases of cataract surgery failure out

of a total of 1182 operated eyes, a frequency of 5.16%, comparable to that of CGF Ngana Ngabou *et al*. which reported 78.95% postoperative visual acuity greater than 3/10. Our result is found in the WHO standard for cataract surgery outcomes [6].

In Africa one of the main difficulties of surgery is access to implants of appropriate power especially implants of low or too high power. In our series, the implant used corresponded to the calculated power in 82% of cases. This result is higher than that of Jw Diallo *et al*., who reported in their 2015 study that the power of the implant used was adequate in 59.67% [7].

The time between studies could be an explanation for this difference. Indeed, the more years pass, the easier access to implants is in developing countries.

Almost all of our patients or 96.72% were over 60 years old. The age group from 60 to 69 years was the most represented with 68.85%. In developing countries and especially in Africa, age is a random factor because many elderly and illiterate people are completely unaware of their ages. This result is different from those of Lindfield R. where the age group of 70 to 79 years was the majority in Bangladesh [8]. Despite the imprecise nature of this variable, it is accepted on the one hand that the vast majority of cataract patients are of the 3rd age and on the other hand that the frequencies of pathologies that can compromise the result of this surgery, such as optic atrophy, Age-Related Macular Degeneration (AMD), diabetic retinopathy, increase with age.

Decreased visual acuity was the main complaint in all our patients either 100% followed by photophobia with 24.4% of cases.

In the history, high blood pressure, present in 8.20% of patients was the most common comorbidity in our series followed by diabetes with 4.92%. Diallo JW *et al*. also reported a predominance of high blood pressure but in a greater proportion with 30.33% of cases [7]. This could be explained by the fact that the frequency of these two pathologies increases with age.

In our series, the causes of failure after cataract surgery were dominated by selection errors which accounted for 36.06% followed by late postoperative complications 34.43%. These results are different from those reported in the literature which attributed one third of complications to inadequate optical correction, one third to selection errors and the last third to postoperative complications. This difference could be explained by the availability in our department of a biometer and implants of various power to minimize refractive errors [8].

Corneal edema and capsular fibrosis were the most observed clinical signs during the biomicroscope examination. This result is close to that of Dolo M who found 28.7% corneal edema [9]. Its occurrence remains frequent in the alternative phaco due to manipulations in the anterior chamber and especially to the manual expulsion of the crystalline nucleus in this technique. These maneuvers can damage the corneal endothelium and thus lead to corneal edema.

Optic atrophy and macular edema were the most common pathologies of the posterior segment with 9.83% each. Macular edema is a common complication

of cataract surgery. However, the early implementation of anti-inflammatory treatment has made it possible to limit its occurrence.

Eye tone was normal in 56 patients (91.80%). We noted two cases of ocular hypertonia (3.28%). Hypertonia is a rare complication after cataract surgery. However in some cases the intraocular pressure or eye pressure increases because the aqueous humor cannot flow freely between the ciliary body, where it is produced, and the trabeculum, where it is excreted.

In our series, 18 patients (29.5%) presented with early postoperative complications such as corneal edema in 15 patients (24.6%) and hyphema in 3 patients (4.9%). Our results are comparable to those of Dolo M *et al*., who in a study conducted in Burkina Faso reported 22.6% of cases of corneal edema and 9.7% of cases of hyphema [9].

Late postoperative complications were dominated by capsular fibrosis encountered in 42.89% of our patients.

Our limitations in this study were diverse both related to the technical platform and to the patients, they were dominated by the non-availability of varied choices of the powers of the implants precalculated during biometrics, the lack of diversification of the choice of the quality of implant according to the visual objective of the patient and its preoperative refraction, the lack of diversified technical platforms for in-depth preoperative examinations, the reception of patients at stages where cataracts were dense thus preventing the examination of the fundus forclinical evaluation and possible functional prognosis after surgery, which limited us through the examinations available to appreciate the posterior segment and to conclude a decision

5. Conclusions

Cataracts are a real public health problem, but they are no longer inevitable nowadays with the advent of intraocular implants and the evolution of different operating techniques, the results are more and more remarkable. Like any surgery, zero risk does not exist in cataract surgery. Some complications may occur in the intraoperative or postoperative period that can affect the functional result of the intervention. In addition to genuine postoperative complications, selection errors, refractive errors and the surgeon's experience are factors that can influence the outcome of surgery.

The complications of cataract surgery pose a challenge. The surgeon’s responsibility is first and foremost to prevent complications. However, despite all the precautions, sooner or later he will face a complication.

By improving the ability to manage complications, they will definitely reduce the number of poor visual outcomes and disappointed patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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SURVEY SHEET

I/ EPIDEMIOLOGY:

■ Name & Surname: .....

■ N°:.....

■ Origin: Rural ☐ Urban ☐

Locality.....

■ Age:..... years ■ Profession:..... ■ Sex: Male ☐ Female ☐

■ Consultation deadline..... Days

II/REASON FOR HOSPITALIZATION

Low visual acuity ☐ Visual fog ☐

Notion of trauma ☐ Photophobia ☐

III/BACKGROUND:

PERSONAL:

-Glaucoma: yes ☐ no ☐

-Another eye diseases: no ☐ if yes ☐ specify.....

-Highpressure concept: yes ☐ no ☐

-Notion of diabetes: yes ☐ no ☐

-Refractive disorders: no ☐ if yes ☐ specify .....

-Medication intake: no ☐ if yes ☐ specify.....

-Smoking: yes ☐ no ☐

-Alcohol: yes ☐ no ☐

-Other flaws: no ☐ if yes ☐ specify.....

FAMILY

-Glaucoma: yes ☐ no ☐

-Other eye diseases: No ☐ if yes ☐ specify.....

-Other flaws: no ☐ if yes ☐ specify.....

VI/CLINICAL EXAMINATION:

A/ ***Ophthalmological examination***:

Affected eye

Visual acuity from far..... from near.....

-Cornea: clear ☐ dystrophic ☐ degenerative ☐

-Anterior chamber: shallow ☐ deep ☐ normal ☐

-Iris: deformedpupil ☐ synechia ☐ myosis ☐

-Crystalline: grade 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

-Intra ocular pressure:

-Vitreous: normal ☐ pathological ☐

-Retina: normal ☐ pathological ☐

Controlateral Eye:

Normal ☐ abnormal ☐ specify.....

B/ ***General examination***

Weight:..... Kg Blood Pressure: ...../.....mm Hg Temperature: ..... ˚C

Breath Frequency:.... Cycle /mn Pulse :..... Batt. /mn

C/***Somatic Examination***:

.....

VII/ ADDITIONAL EXAMINATIONS:

Ultrasound: normal ☐ pathological ☐

Biometrics:

***K*1**

***K*2**

The

***IOL*1**

***IOL*2**

VIII/ TYPE OF SURGERY

EEC ☐ **Phaco A** ☐

VIII/ COMPLICATIONS:

A-Early complications

1-Corneal complications

Tears of cemetics ..... ☐

Corneal edema..... ☐

Loss of endothelial cells..... ☐

2-Hemorrhagic complications..... ☐

3-Irian complications

Hernia of the iris..... ☐

Lesions of the iris sphincter ..... ☐

Disinsertion of the root of the iris..... ☐

4-Previous capsular complications: Yes ☐ No ☐

5-Posterior capsular complications

Limited opening..... ☐

Complete tear..... ☐

Dislocation of the complete nucleus..... ☐

Dislocation of nucleus fragments..... ☐

6-Zoular complications..... ☐

7-Expellive hemorrhage..... ☐

8-Acute endophthalmitis..... ☐

B-Late complications

1-Capsular opacification:

Fibrosis..... ☐

beads..... ☐

capsulophimosis..... ☐

2-Corneal decompensation..... ☐
3-retinal detachment..... ☐
4-Macular edema..... ☐
5-Chronic endophthalmitis.....☐

IX RESULTS:

Functional: Visual acuity Day1st ..... Day7th ..... Day30th .....

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Crowned Dens Syndrome: Recent Progress on Diagnosis and Treatment

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Abstract

Defined as an association of acute cervical pain and calcifications in the peri-odontoid space, crowned dens syndrome (CDS) is a major imaging manifestation of "coronary". CDS is a rare but under-recognized cause of severe neck pain in older adults. As such, it is often misdiagnosed. So, we review the literature with particular attention to the clinical and radiological aspects of this syndrome.

Keywords

Crowned Dens Syndrome, Radiology, Calcification, Computed Tomography, Nosogenesis

1. Introduction

In 1985, crowned dens syndrome (CDS) was first described by Bouvet *et al.* [1]. The pathogenesis is widely believed to be caused by crystal deposition disease [2] [3]. On radiographic images, calcium salt deposition around the odontoid is seen, mainly on the posterior side, like a crown on the odontoid process, from which it got the name. Clinical manifestations are mostly sudden neck pain and muscle joint stiffness, with limited neck movement. There are also chronic onset or acute-on-chronic onset [4] [5]. CDS often has a good prognosis [6]. In the foreign research [7], 2556 cases cervical CT plain scans were screened, among which 69 were diagnosed with calcification around odontoid process, demonstrating that this phenomenon was not rare. According to incomplete statistics,

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#Wei Hu, Cheng Li, Xingming Lai, Jinpeng Zheng, Nian Liu contributed equally to this paper.

the incidence of CDS can be as high as 45% in the elder population over 85 years old [8]. However, due to little understanding of CDS, misdiagnosis or missed diagnosis often occurs in daily clinical work, causing unnecessary examination or treatment, and delaying the diagnosis and treatment of the disease. In this paper, the research status of CDS was discussed based on individual cases, theoretical works and reviews published at home and abroad in recent years, combined with actual clinical work.

2. Etiology and Pathogenesis

2.1. Crystal Deposition

At present, most scholars believe that crystal deposition may be the main cause of CDS, which is mainly related to the deposition of CPPD crystals (calcium pyrophosphate dihydrate deposition disease, CPPD) and HA crystals (hydroxyapatite, HA). Some scholars believe that CDS is caused by the abnormal deposition of bone salt caused by the abnormal activity of osteoblasts. However, in the CDS cases reported at home and abroad at present, the incidence of CDS caused by CPPD deposition is far more than that of HA deposition. Scutellari [3] *et al*. found through CT scan results calcification deposits in the check ligament, transverse atlas ligament, odontoid ligament and ligamentum flavum in 12 patients (3 males and 9 females), with horseshoe-shaped or coronal calcification around the odontoid process. Scutellari *et al*. suggested that the deposition of HA crystals could cause CDS, but it was rare and only middle-aged women seemed to be affected. H Cox *et al*. [9] performed CT scan on a 74-year-old male patient with sudden neck pain and limitation of motion, and found soft tissue calcification in the ligament around the atlas. There was also radiographic evidence of diffuse idiopathic skeletal hyperostosis (DISH). Kandel found an association between CPPD and DISH in his study of ape populations in the Barbary region of North Africa, but this phenomenon has not been confirmed in humans [10].

2.2. Gender and Age Factors

According to numerous case reports and relevant literature on CDS at home and abroad, its occurrence seems to be highly related to age and gender, and the higher the age, the higher the incidence, mostly occurring in elderly women over 60 years old [11]. Lu [7] *et al*. analyzed the CT of 2556 patients and found that 69 cases were diagnosed with calcification around odontoid process and 19 with CDS, most of which were elderly female patients over 65 years old. Okazaki *et al*. [12] reviewed 72 cases, including hospitalized patients and case data published on the Internet, and calculated that the average age of CDS was 71 years old in accordance with their data. Most of the patients admitted for acute neck pain and neck stiffness with activity limitation and finally diagnosed with CDS were elderly women [13]. Sano *et al*. [14] performed cranial CT scan on 577 patients with intracerebral hemorrhage or subarachnoid hemorrhage hospitalized

in neurosurgery department, and found calcification around odontoid process in 88 patients (15.9%), including 32 males and 56 females. The prevalence of odontoid calcification was higher in women than in men. Although patients undergoing cranial CT scans varied in age, CDS was mostly found in patients older than 60 years. At the same time, Goto *et al*. [15] found that CDS was more common in Asians, especially in elderly women, with a male-female ratio of about 0.6 and 2/3 CDS patients were older than 70 years old. Oak [12] believed that hormone levels were related to calcifications surrounding the odontoid process. Decreased estrogen production in postmenopausal women promoted bone resorption and an increase in intra-articular calcium, leading to an abnormal deposition of calcium salts and crystals. Mula and Malca also found that in CDS patients, the proportion of CPPD deposition was much higher than that of HA deposition. Meanwhile, the number of reported cases in males was much smaller than in females [16] [17].

2.3. Other Factors or Conjectures

At present, CDS is still in the stage of exploration and empiric therapy, and clinical researchers at home and abroad have put forward a series of conjectures or hypotheses. The current mainstream view, namely inflammation theory, believes that crystal deposition can cause aseptic inflammation while compressing and stimulating the C1 and C2 nerve roots. Acute and severe pain can be caused by neck muscle tension, muscle contraction or neck movement [18]. However, in the actual clinical work, it is undeniable that some patients have no typical symptoms of CDS such as pain or limited mobility, or even no symptoms at all. For them, CDS is detected by accident during the examination of other diseases or routine physical examination. Therefore, the simple inflammation theory cannot fully explain the etiology and symptoms of CDS. Studies have shown that high calcium, high phosphorus and low magnesium, joint wound, hypothyroidism, hyperlactinemia, hypertriglyceridemia, hemochromatosis, severe anemia, diabetes, cerebral infarction, intraparenchymal hemorrhage, subarachnoid hemorrhage, Wilson disease, postmenopausal syndrome, severe osteoporosis, myocardial infarction, systemic inflammatory response, or other major internal and surgical diseases may become high risk factors of CDS. Zhang *et al*. [19] pointed out that the occurrence and development of CDS might be related to diabetes with poor blood glucose control for many years. Nakano *et al*. [20] reported a unique case of CDS after endoscopic retrograde cholangiopancreatography (ERCP) in 2016, in which the patient mainly had a fever and neck pain. Considering that excessive mechanical load of neck movement may be a factor triggering CDS, it might be caused by joint injury resulting from limited cervical rotation when the patient was in prone position in the ERCP. Sano *et al*. [14] performed head CT scan on 577 patients with cerebral hemorrhage or subarachnoid hemorrhage hospitalized in the neurosurgery department, and calcification around odontoid process was found in 88 patients (15.9%). They were

more likely to get CDS than normal patients, indicating that severe systemic inflammation caused by critical illness could increase the incidence of CDS. Zunkeler *et al*. [21] assumed that systemic CPPD deposition was clinically associated with a variety of metabolites, including hyperphosphatemia and Wilson's disease. Zunkeler *et al*. also believed that factors such as age, genetics and various muscle stress imbalance might also promote CPPD crystal formation. Sugihara *et al*. [22] claimed that the occurrence and development of CDS might be associated with hyperuricemia. In 2000, Ho *et al*. [23] found ANK gene, meaning progressive ankylosis, in the study of mouse mutant strains with severe ankylosis of spine and other joints. The ANK gene was cloned to obtain a human homolog called ANKH gene. Preliminary studies show that ANK is a transporter of inorganic pyrophosphate (PPi), a potent inhibitor of hydroxyapatite mineralization. Therefore, it is speculated that the loss of ANK/ankmice translocator function leads to the loss of PPi transport function in the affected animals, thus resulting in excessive mineralization. Further biochemical studies of ANK function in frog oocytes performed by Gurleyet [24] showed that the ANK/ANK mutation (E440X) led to a significant decrease or even loss of PPi transport activity, which might be one of the causes of CDS. However, the specific mechanism of ANKH gene needs to be further studied.

3. Clinical Manifestations, Diagnosis, and Differential Diagnosis

Crowned dens syndrome is a special case of pseudogout that occurs in the atlantoaxial joint [25]. Its typical clinical manifestations include acute neck pain (100%), neck stiffness with confined movement (98%), and some cases may be accompanied by fever and chills (80.4%) and other symptoms [12]. There have also been reports of cases with chronic neck pain as the chief complaint and eventually diagnosed with CDS [4] [5], and such chronic cases are easily misdiagnosed as common diseases such as cervical spondylosis. Zhang *et al*. [19] reported a case of advanced CDS, for which the X-ray showed diffuse odontoid calcification and destructive intervertebral disc lesions and joint. In a few cases, aseptic inflammation will gradually erode the atlantoaxial ligament, and even form a cavity, leading to atlantoaxial instability, spinal cord compression and progressive tetraplegia, forming symptoms similar to cervical spondylosis, such as root symptoms of the upper limb, walking difficulties, stumbling gait, acragnosis and other symptoms [26].

Currently, CDS is mostly clinically diagnosed by CT, which is taken as the "golden standard". Studies have shown that the detection rate of CT in the diagnosis of CDS is as high as 97.1% [12], which can clearly show the high-density calcification shadow around the odontoid process, and assess the degree of its calcification. So its diagnosis is mainly based on the typical clinical manifestations and CT. Flurodeoxyglucose (18F-FDG) labeled with fluoro-18 is a new contrast agent based on radionuclide imaging technology, and its diagnostic

value for fever of unknown origin has received gradual attention in recent years [27]. Its diagnosis covers a wide range and can show aseptic inflammatory calcium deposition surrounding the odontoid process. However, 18F-FDG PET/CT is not the first choice due to its high cost, cumbersome operation and low popularity rate. Goto [16] summarized the possibility of CDS calcification occurring at different locations of the odontoid process in accordance with numerous radiographic data: posterior (50%), posterolateral (27.5%), annular (12.5%), anterior (5%) and lateral (5%). Since the calcification of CDS is more common in the rear of the odontoid process, it is difficult to clearly show the local calcification with X-ray in the diagnosis of CDS due to the overlapping radiography, so plain X-ray film examination and diagnosis is of little significance. MRI is better than CT in showing local inflammatory changes, and can determine whether there is nerve compression, but it is less sensitive to calcifications than CT [28]. A large number of actual clinical cases also suggest that X-ray and MRI are far less valuable in CDS diagnosis than CT. CDS cases showed elevated levels of serum inflammatory markers in laboratory tests, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell ratio [29]. The detection rate of serum inflammatory markers was about 88.3% [12], while procalcitonin did not increase. Some patients with CDS often have pseudogout gout [25] in the knee joint and hip joint, so the discovery of crystal deposition by puncture examination can also be considered as one of the diagnostic basis.

Although CDS is not a rare disease, it is prone to misdiagnosis and missed diagnosis because of the lack of understanding in practical work. It is necessary to distinguish it from some common diseases. The most important differential diagnose is meningitis, whose clinical manifestations are very similar to those of CDS, such as neck pain, stiffness, fever, etc. One of the important bases of meningitis is that MRI shows a nodular or thickened line-like enhancement [30]. Meningeal lesions should be taken into account when the length of meningeal enhancement is greater than 3 cm [31]. CDS did not show meningeal changes on imaging, and the deposition of CPPD crystals also helped to exclude meningitis. Cervical myofascial pain syndrome also has similar clinical manifestations as crowned dens syndrome, which can also be seen as elevated levels of serum inflammatory markers. However, this disease often results from cervical myofascial overwork or acute trauma, and cords can be felt in the affected area during a physical examination, which can be alleviated after manual massage [32]. The typical clinical manifestations of polymyalgia rheumatica (PMR) are stiff and painful neck, shoulder and hip muscles, and limited upper limb lift. Almost all patients (95%) have shoulder fatigue, and neck fatigue accounts for approximately 70% [33]. PMR can also be accompanied by low fever, tiredness, drowsiness, systemic muscle soreness, anorexia, weight loss and other non-specific systemic manifestations [34]. These are not found in the cases of CDS. CDS also requires differential diagnose with rheumatoid arthritis, gout, discitis, cervical spondylosis and neck muscle strain.

4. Current Treatment of CDS

At present, non-steroidal anti-inflammatory drugs (NSAIDs) or hormones are mainly used in the treatment of CDS, but which type is the first choice is still controversial. NSAIDs are recommended as first-line therapy in most cases reported in the literature, and symptoms usually improve within a few days after oral administration of NSAIDs. Oka *et al*. [13] believed that the use of NSAIDs could effectively and rapidly relieve pain and activity limitation and other symptoms. In 1995, Malca [18] *et al*. used diclofenac intramuscular injection treatment and achieved good analgesic effect.

Low-dose hormone (15 - 30 mg) was also recommended by some literature [35] as the first-line drug, which has achieved ideal curative effect. Therefore, it can be considered for patients who are intolerant to NSAIDs or who do not respond to NSAIDs treatment. CDS is more common in elderly patients, and their use of hormone drugs may lead to osteoporosis, femoral head necrosis, infection and other serious complications. Therefore, it is necessary to consider whether there are contraindications to hormone therapy in combination with the actual situation of the patients before careful medication, and long-term use is not recommended [36]. However, some studies have shown [37] that hormone drugs are better than NSAIDs in terms of efficacy, with which the symptomatic relief is more pronounced and lasting. Valnet suggested the combination of NSAIDs drugs and low-dose hormones as the best treatment for CDS [37].

Colchicine appears to be effective in some cases of refractory CDS, but its efficacy is less certain than that of NSAIDs or hormones. In addition, colchicine has slow onset and long treatment cycle, and may be accompanied by severe complications such as diarrhea, so it is not considered as the drug of choice. Risk factors for CPPD deposition, such as low magnesium, hyperparathyroidism, hyperglycemia and other complications should also be addressed.

The dialectical thinking of traditional Chinese medicine regards CDS as xiang bi disease (cervical spondylosis), which is caused by qi stagnation and blood stasis, and obstruction of meridians. Clearing wind-damp to relieve pain is required. Qianghuo Shengshi Soup (literal meaning of soup made of notopterygium root to dispel dampness) can be used as the prescription for clearing wind-damp, dredging the channels and collaterals and relieving pain [38].

5. Summary

To sum up, CDS is prone to misdiagnosis and missed diagnosis due to its unclear pathogenesis, relatively simple diagnosis method and less exposure at work. Ho *et al*. [23] reported the effect of ANK gene on crystal deposition in mice, so ANKH gene may be the key to the development of targeted drugs in the future. Patients with CDS often go to the emergency department because of acute neck pain, and its incidence can be as high as 45% in the elderly population over 85 years old. In most cases, CDS has a good prognosis, and the condition can be relieved within a few weeks after correct treatment, but attention should also be

paid to the possibility of protracted course or further aggravation of the disease. Therefore, early diagnosis and timely treatment are particularly significant to avoid unnecessary tests and treatment or delay of the illness.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Efficacy and Safety of 30% Supramolecular Salicylic Acid Peeling Combined with Isotretinoin Erythromycin Gel in the Treatment of Moderate-to-Severe Acne Vulgaris: A Comparative Study

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Abstract

Background: Both 30% supramolecular salicylic acid (SA) and isotretinoin erythromycin gel (IEG) have proven efficacy with good safety profiles in the treatment of acne vulgaris. **Objectives:** This study compared the clinical efficacy and safety of 30% SA peeling and IEG in the treatment of moderate-to-severe acne vulgaris. **Methods:** Patients with moderate-to-severe acne vulgaris were randomized into 3 groups of 30 persons each, and treated with SA peel, or IEG, or SA combine with IEG (SA + IEG group). Evaluation of acne was done by effective rate and individual lesion counts. And the adverse effects and recurrence were recorded. **Results:** The SA + IEG group was better in clinical efficacy and treating noninflammatory and inflammatory lesions than that of single treatment group ($P < 0.05$). No serious adverse effects were recorded. There were no significant differences in adverse effects and recurrence between groups ($P > 0.05$). **Conclusion:** 30% SA combined with IEG had a significant effect in the treatment of moderate-to-severe acne lesions.

Keywords

30% Supramolecular Salicylic Acid, Isotretinoin Erythromycin Gel, Moderate-to-Severe Acne Vulgaris, Efficacy, The Adverse Reactions, Recurrence Rate

1. Introduction

Acne vulgaris is a common chronic inflammatory disease involving follicles and

sebaceous glands [1]. It often occurs in the rich part of sebaceous glands, characterized by comedones, papules, pustules, cysts or nodules [2]. Because acne vulgaris is easy to relapse, patients' compliance is poor, which is easy to cause psychological burdens and social problems [3]. Therefore, seeking effective, safe and easy to be accepted by patients has become the focus of clinical research.

In recent years, our department has adopted a new 30% SA to achieve certain efficacy in the treatment of mild-to-moderate acne. IEG is effective in regulating the keratosis of sebaceous ducts of follicles and controlling microbial infection and inflammatory reaction. At present, the focus of SA technology is on the treatment of mild acne, and the research on the treatment of moderate-to-severe acne is just starting. In this study, 30% SA combined with IEG was used to treat patients with moderate-to-severe acne. The results are reported as follows.

2. Material and Methods

The study was approved by the ethics committee of Zhuji People's Hospital. Written informed consent was obtained from all patients (older than 18 years) in this study.

2.1. Patient Selection

90 patients with acne who came to the author's department from January 2022 to June 2022 were selected as the study population.

Inclusion criteria: the severity of skin lesions was grade II-IV according to the international Pillsbury classification of acne (grade II and III were moderate and grade IV was severe); in the past 2 months, no acne drugs have been used and no chemical peeling has been carried out; good compliance, able to complete treatment, and regular follow-up; the subjects understood the purpose and content of the study and signed the informed consent.

Exclusion criteria: patients with photosensitive history; patients with skin diseases such as eczema or psoriasis on the face; suffering from other serious medical diseases, tumors or mental diseases; pregnant and lactating women; scar constitution; allergic to salicylic acid; there were other factors affecting this study.

2.2. Treatment

The patients were divided into three groups of 30 each, based on a random number method: the first group (SA group) was treated with 30% SA peels (Broda, Shanghai Ruizhi Pharmaceutical Technology Co.) alone once every 2 weeks, a total of 4 times [4] [5]; the second group (IEG group) was treated with IEG (Tongnuo, Sinopharm Group Zhonglian Pharmaceutical Co.) alone twice a day for 8 weeks; the third group (SA + IEG group) was treated with 30% SA peels once every 2 weeks, 4 times in total, and coated with IEG twice a day for 8 weeks. Clinical evaluation was performed every 2 weeks throughout the study period. In the SA group, the end point was when erythema or frosting reaction occurred locally on the skin. After reaching the end point, rinse with cold water,

and ice pack for 15 min.

2.3. Clinical Assessment of Efficacy

At baseline and at each follow-up, clinical photos of the patients were taken including the front, left and right faces. The improvement of lesions was evaluated: counted the number of noninflammatory lesions (comedones) and inflammatory lesions (papules and pustules), and calculated the efficacy index according to the reduction in mean lesions between baseline and 8 weeks. Judgment standard of efficacy index was cure (≥90%), significant effect (60% - 89%), effective (20% - 59%), invalid (<20%). Effective rate = cure + significant effect.

2.4. Assessment of Adverse Effects

The adverse reactions of patients during treatment and follow-up were recorded, such as erythema, edema, pain, pruritus and the total number of cases.

2.5. Assessment of Recrudescence

One month after the end of treatment, we followed up the patients by telephone to see if they had new lesions. If the number increased by more than 10%, it was considered as recurrence.

2.6. Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Microsoft Windows 20th version was used for statistical analysis. For the comparison of nominal or continuous data such as age distribution, individual lesion count between the groups, variance test was used. Categorical data, *i.e.*, sex of the patients, improvement in acne, adverse effects, recrudescence in each group, were compared using the chi-squared test. The tests were performed at a 5% level of significance and an association was found to be significant if the P value was <0.05.

3. Results

A total of 90 patients were randomly treated with 30% SA or/and IEG. There was no statistically significant difference between the three groups in age distribution, gender, and the average noninflammatory lesions and inflammatory lesion counts at baseline, which was comparable (**Table 1**).

3.1. Evaluation of Clinical Efficacy

After 8 weeks of treatment, the patients in the three groups all achieved good efficacy. Lesions in the three groups were effectively controlled. The effective rate of SA + IEG group (76.7%) was significantly higher than that of SA group (43.3%) and IEG group (40.0%), indicating that the efficacy of SA + IEG group was better than that of SA group and IEG group. The difference between the groups was statistically significant ($P < 0.05$) (**Table 2**). Typical case was shown in **Figure 1**.

Table 1. Baseline characteristics of the 90 patients with acne vulgaris.

	SA group (n = 30)	IEG group (n = 30)	SA + IEG group (n = 30)	P*	P#
Age (years), mean (SD)	24.6 (4.8)	24.7 (4.0)	24.4 (4.6)	0.95	0.81
Sex, n				0.43	0.57
Male	13	8	10		
Female	17	22	20		
Noninflammatory lesions, mean (SD)	38.27 (7.94)	37.49 (6.32)	38.12 (7.30)	1.00	0.13
Inflammatory lesions, mean (SD)	33.82 (9.73)	33.05 (9.10)	33.11 (9.07)	0.28	1.00

SA = salicylic acid; IEG = isotretinoin erythromycin gel; SD = standard deviation; P* = SA group vs SA + IEG group; P# = IEG group vs SA + IEG group.

Table 2. Clinical efficacy of acne patients after 8 weeks of treatment.

Group	Cure, n (%)	Significant effect, n	Effective, n (%)	Invalid, n (%)	Effective rate (%)
SA group (n = 30)	1 (3.3)	12 (40.0)	15 (50.0)	2 (6.7)	43.3
IEG group (n = 30)	0 (0.0)	12 (40.0)	13 (43.3)	5(16.7)	40.0
SA + IEG group (n = 30)	4 (13.3)	19 (63.3)	7 (23.3)	0 (0.0)	76.7
P*					<0.05
P#					<0.05

P* = SA group vs SA + IEG group; P# = IEG group vs SA + IEG group.

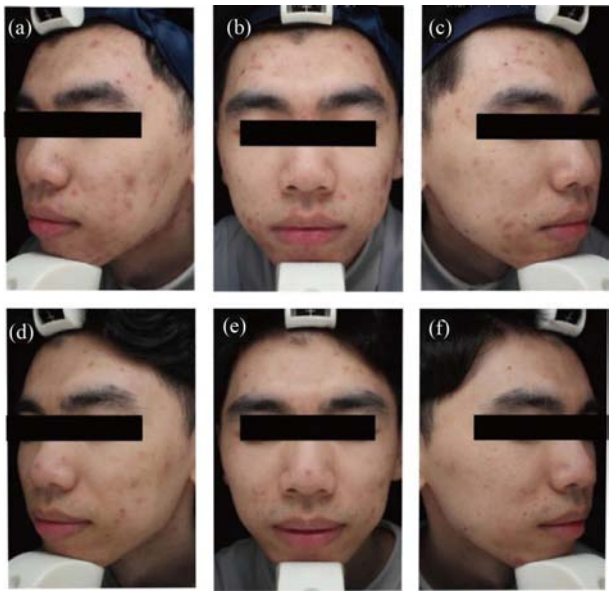

Figure 1. Images (a) (b) (c) and (d) (e) (f) show the baseline and 8-week results with SA + IEG combination therapy.

Regarding the comparison of the number of lesions in the three groups before and after treatment, there was no significant difference in the number of noninflammatory lesions and inflammatory lesions in the three groups before treatment ($P > 0.05$). After 8 weeks of treatment, the number of acne lesions in the three groups decreased. The comparison between groups showed that the number of noninflammatory lesions and inflammatory lesions in SA + IEG group after 8 weeks of treatment was significantly lower than that before treatment ($P < 0.05$). This indicated that the combination of SA and IEG was better than that of SA and IEG alone (Table 3).

3.2. Adverse Effects

During the treatment and follow-up, the adverse reactions were mainly erythema after peeling, local tingling, itching and dryness. The number of cases in the combined group (n = 4) was less than that in SA group (n = 6) and IEG group (n = 5), but the difference was not statistically significant ($P > 0.05$). Local strengthening cold compress external application of moisturizing agent could relieve discomfort.

3.3. Recrudescence

One month after the end of treatment, 3 patients in SA + IEG group recurred, with a recurrence rate of 10.00%, 5 patients in SA group recurred, with a recurrence rate of 16.67%, 8 patients in IEG group recurred, with a recurrence rate of 26.67%. The recurrence rates of the three groups were low. There was no statistical difference between the combined group and the other two groups ($P > 0.05$).

4. Discussion

Excessive sebum secretion, abnormal keratosis of sebaceous ducts in follicles, infection of microorganisms (especially Propionibacterium acnes) and inflammatory reaction are all important factors that cause the occurrence and development of acne vulgaris. In general, lipid suppression, keratinization regulation

Table 3. Comparison of the difference in the number of lesions in acne patients before and after treatment.

Group	Difference in the number of noninflammatory lesions, mean (SD)	Difference in the number of inflammatory lesions, mean (SD)
SA group (n = 30)	23.50 (7.84)	24.02 (9.30)
IEG group (n = 30)	23.16 (7.99)	18.92 (8.77)
SA + IEG group (n = 30)	30.76 (9.31)	24.19 (10.04)
P*	<0.05	<0.05
P#	<0.05	<0.05

P* = SA group vs SA + IEG group; P# = IEG group vs SA + IEG group.

and anti-infection can play a therapeutic role [6]. However, compared with traditional oral antibiotics, retinoic acid and other drugs, external treatment can eliminate patients' concerns about oral medication [7] [8].

30% SA peeling is a kind of surface peeling treatment for acne, which tends to mature [9]. Its efficacy has been confirmed by some studies [10] [11] [12]. SA preferentially acts on the sebaceous gland unit and has strong anti-inflammatory, antibacterial and keratinization regulating properties [13]. IEG has the functions of reducing sebum secretion, inhibiting keratinocyte proliferation, preventing keratin embolism, reducing pathogenic bacteria related to the etiology of acne, reducing the inflammatory reaction at the lesion site and so on, so as to make acne lesions disappear [14].

Our study included 90 patients with moderate-to-severe acne vulgaris. Objective evaluation of acne treatment by effective rate and individual lesion count showed that after 8 weeks, the effective rate of combined treatment group was significantly higher than that of single treatment group, and the number of noninflammatory lesions and inflammatory skin lesions decreased significantly better than that of single treatment group, suggesting that SA has the characteristics of anti-inflammatory, anti-bacterial, dissolving fat thrombus and reducing oil secretion. The application of IEG, which could further improve the aggravation of pustules during SA treatment, reduce irritation and reduce adverse effects, and could be used for maintenance treatment during chemical peeling [15].

5. Conclusion

To sum up, 30% SA combined with IEG had a significant effect in the treatment of moderate-to-severe acne lesions. This experiment had not caused serious adverse reactions had high safety and low recurrence rate. It is a good treatment method and is worthy of clinical promotion.

6. Limitations

The sample size was small, keeping in mind the patient compliance because of the multiple peeling sessions required in the study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Relationship between Radiological Lung Findings and Laboratory Ferritin and D-Dimer Levels in Patients with COVID-19 Infection

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Abstract

Introduction: Pulmonary symptoms of COVID-19 infection range from asymptomatic infection to severe pneumonia. Pathogenesis and severity of symptoms were found to be related to the body's immune response. **Objectives:** Ferritin and D-Dimer in COVID-19 confirmed cases can predict lung injury and possible poor patient prognosis. **Materials and Methods:** Patients who had been admitted to Dr. Sulaiman Alhabib-Arryan Hospital with positive COVID-19 polymerase chain reaction (PCR) tests between March 2020 and December 2021 were studied for blood ferritin and D-Dimer levels in relation to pulmonary radiological findings. **Results:** A total of 494 cases are included in this study. Male patients represent 74.1% of the cases, and the mean age is 51.68 ± 13.37 years. Increased age, ferritin, D-Dimer levels, and respiratory symptoms are factors that showed a statistically significant association with positive computed tomography (CT) findings. Receiver operator characteristic curve (ROC) showed that ferritin has a higher capability than D-Dimer to detect CT findings and that both are equal in predicting possible patient mortality. Suggested cutoff values for Ferritin > 336 ng/mL, with 78.21% sensitivity and 86.42% specificity and for D-Dimer > 0.55 mg/L FEU, with sensitivity of 74.82% and specificity of 75.31%. For mortality, the suggested cutoff point for ferritin is >864.6 ng/mL, which gives a sensitivity of 80.26 and a specificity of 64.83%. The suggested cutoff point for D-Dimer is >1.46 mg/L FEU, which gives a sensitivity of 65.79% and a specificity of 78.23%. **Conclusion:** Laboratory markers such as Ferritin and D-Dimer can be an accurate predictor of lung injury in COVID-19 patients and their increased values can predict the poor patient prognosis and possible mortality if aggressive hospital care is not provided.

Keywords

Ferritin, COVID-19, D-Dimer

1. Background

Outbreaks of COVID-19 infection started to affect the world since last 2019 when it erupted in Wuhan, China and then the whole world. The WHO considered it a worldwide pandemic in March 2020 [1] [2].

Symptoms of COVID-19 infection range from asymptomatic infection to severe pneumonia, sepsis, acute respiratory distress syndrome and mortality due to respiratory failure and multi-organ dysfunction [2] [3].

The pathogenesis and severity of symptoms were found to be related to the body's immune response that will affect many body systems, including the hematological, epithelial, and vascular system [4].

Lung and vascular injuries occur secondary to the release of large amounts of inflammatory cytokines [4]. Virus replicating in respiratory epithelial cells will result in release of large amounts of these cytokines, causing severe lung disease [5].

The condition of the high inflammatory cytokines in the circulation of COVID-19 patients is known as cytokine storm. This storm is strongly associated with symptoms severity. Interleukins 2, 6, 7 and 10, TNF α and interferon γ [1] [3] [4] [5], are examples of some of those mediators. This rise in the inflammatory cytokines and associated apoptosis are the main causes of lymphopenia observed in COVID-19 patients, which was a feature in the severely ill and many hospitalized patients [6] [7] [8].

This massive release of inflammatory cytokines in COVID-19 patients is also associated with activation of the coagulation pathway and elevation of serum ferritin, making COVID-19 one of the causes of hyperferritinemic syndrome [9].

Activation of the coagulation pathway will cause arterial and venous thrombosis that will be aggravated by the presence of co-morbidities such as hypertension, lung disease, and diabetes [10].

Elevation of inflammatory biomarkers such as C-reactive protein (CRP), D-Dimer, procalcitonin, ferritin, lactate dehydrogenase (LDH) and interleukin-6 (IL-6) are found to be associated with severe COVID-19 infection [10].

Imaging studies gained by using computed tomography (CT) scan are considered a sensitive method for early detection of lung injury in pneumonia. Most CT findings are in the form of ground glass opacity (GGO), with or without consolidation, interlobular septal thickening, lymphadenopathy, and pleural effusion [10].

Aim of the Work

The present study was designed to clarify the diagnostic accuracy of using laboratory markers such as ferritin and D-Dimer in COVID-19 confirmed cases to

predict lung injury and to limit the unnecessary use of radiological investigations (CT scans), thus decreasing the burden of its usage in diagnosing lung involvement in COVID-19 cases, especially during pandemic situations. This would decrease the time patients spend in the triage area waiting for CT results.

2. Methodology

2.1. Study Design

Observational retrospective Cohort study was performed after ethical approval was obtained from the Institutional Review Board (IRB) of Dr. Sulaiman Alhabib Medical Group, holding approval number HAP-01-R-082. No consent was needed.

2.2. Study Population

The study was performed on patients who had been admitted to Dr. Sulaiman Alhabib-Arryan with a positive COVID-19 PCR test.

2.3. Study Subject

Data was collected from patients confirmed to have positive COVID-19 Real Time Polymerase Chain Reaction (RT-PCR) test at time of admission to Dr. Sulaiman Alhabib-Arryan Hospital in the duration between March 2020 and December 2021. Test done by utilizing specific and sensitive Nucleic Acid Amplification Techniques (NAAT)/(RT-PCR). The viral genes targeted are E, N, and RdRp/ORF. The sample was collected using a nasopharyngeal swab and viral RNA was extracted and subjected for testing to confirm the presence of the known gene sequence/s of SARS-CoV-2 Virus in the designated samples. Inclusion criteria of adult patients with age ranging from 18 - 75 years old, with available pulmonary CT, and laboratory result for ferritin and D-Dimer. The exclusion criteria were patients aged more than 75 and less than 18, pregnant females, any patient with iron deficiency anemia and any hyperferritinemic states such as sepsis due to bacterial, fungal or viral sources other than COVID-19, iron overload due to hemochromatosis or chronic transfusions, and chronic hemolytic anemia. Radiological and laboratory findings are collected from available data in the hospital information system (VIDA).

2.4. Study Variables

Patients were positive for COVID-19 by RT-PCR.
Pulmonary CT findings.
Ferritin.
D-Dimer.

2.5. Data Collection/Data Source

Data was collected from the hospital information system (VIDA) in Dr. Sulaiman Alhabib-Arryan Hospital. Collected data included age, gender, date of ad-

mission, respiratory symptoms, comorbidities relevant to COVID-19 infection, laboratory results of ferritin, D-Dimer, and pulmonary CT findings. Respiratory symptoms include dyspnea, chest pain, shortness of breath, or cough. Comorbidities that may worsen patient's outcome include diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), and chronic lung diseases. Radiological images were examined by an experienced radiologist for the presence or absence of any findings significant for COVID-19 pneumonia in the form of either unilateral or bilateral ground glass opacities (GGOs), parenchymal consolidations, septal thickening, pleural effusion, or enlarged mediastinal lymph nodes (11).

2.6. Statistical Analysis

Descriptive statistics are presented in the form of mean with standard deviation or median with Q1 and Q3 for numeric variables, while frequencies and percentages are used for categorical variables. Multiple logistic regression for the factors associated with positive CT findings while controlling for other variables. Receiver operating characteristic (ROC) curve with area under the curve (AUC) were used to study the diagnostic ability and get the suitable cutoff points with corresponding sensitivity and specificity. The IBM SPSS Version 28 software for Windows was used for the statistical analysis, and MedCalc Version 20 was used for developing the ROC curves.

3. Results

A total of 494 cases are included in this study. Male patients represent 74.1% of the cases, and the mean age is 51.68 ± 13.37 years. 47.4% of the patients had comorbidities, and 80.8% had respiratory symptoms. 83.6% had positive CT findings, and mortality was observed in 15.4% of the cases. The median ferritin level for the patients was 691.71 ng/mL (Q1, Q3: 225.29 ng/mL, 1443.09 ng/mL), and the median D-Dimer level was 0.88 mg/L FEU (Q1, Q3: 0.45 mg/L FEU, 1.87 mg/L FEU) (Table 1).

Multiple logistic regression for the factors associated with positive CT findings while controlling for other variables. The factors that showed statistically significant associations with positive CT findings are age, having respiratory symptoms, ferritin, and D-Dimer levels. Higher age is associated with higher odds of having positive CT findings (OR = 1.028, 95% CI: 1.005% - 1.052%), p-value = 0.018. Those with respiratory symptoms have higher odds for positive CT findings as compared to those with no respiratory symptoms (OR = 4.573, 95% CI: 2.436% - 8.585%), p-value < 0.001.

Higher ferritin level is associated with higher odds of having positive CT findings (OR = 1.002, 95% CI: 1.001% - 1.003%), p-value < 0.001. Higher D-Dimer level is associated with higher odds of having positive CT findings (OR = 1.612, 95% CI: 1.053% - 2.465%), p-value = 1.612 (Table 2).

ROC curve (Figure 1), is used to study if ferritin or D-Dimer can be used to

Table 1. Characteristics of the study sample.

		N	%
Gender	Female	128	25.9
	Male	366	74.1
Age in years.	Mean (SD)	51.68 (13.37)	
Comorbidities	No	260	52.6
	Yes	234	47.4
Respiratory symptoms	No	95	19.2
	Yes	399	80.8
CT findings	No	81	16.4
	Yes	413	83.6
Mortality	No	418	84.6
	Yes	76	15.4
Ferritin (ng/mL)	Median (Q1, Q3)	691.71 (225.29, 1443.09)	
D-Dimer (mg/L FEU)	Median (Q1, Q3)	0.88 (0.45, 1.87)	

Table 2. Multiple logistic regression for the factors associated with positive CT findings.

	Odds ratio	P-value	95% CI for odds ratio	
Age	1.028	0.018	1.005	1.052
Respiratory symptoms				
No	1			
Yes	4.573	<0.001	2.436	8.585
Ferritin	1.002	<0.001	1.001	1.003
D-Dimer	1.612	0.028	1.053	2.465

CI: Confidence Interval.

predict positive CT findings and to get the corresponding cutoff points with sensitivity and specificity. Ferritin showed better diagnostic capability as compared to D-Dimer as it has higher AUC (0.891) as compared to that of the D-Dimer (0.783), p-value < 0.001 (**Table 3**).

ROC curve is used to study if ferritin or D-Dimer can be used to predict mortality and to get the corresponding cutoff points with sensitivity and specificity (**Figure 2**). Ferritin showed no difference in diagnostic capability as compared to D-Dimer as its AUC (0.781) was not different from that of the D-Dimer (0.799), p-value = 0.584 (**Table 4**).

For positive CT findings, the suggested cutoff point for ferritin using Youden's index is >336 ng/mL, which gives a sensitivity of 78.21% (95% CI: 73.9% - 82.1%), and a specificity of 86.42% (95% CI: 77.0% - 93.0%). The suggested cutoff point for D-Dimer using Youden's index is >0.55 mg/L FEU, which gives a sensitivity of 74.82% (95% CI: 70.3% - 78.9%) and a specificity of 75.31%

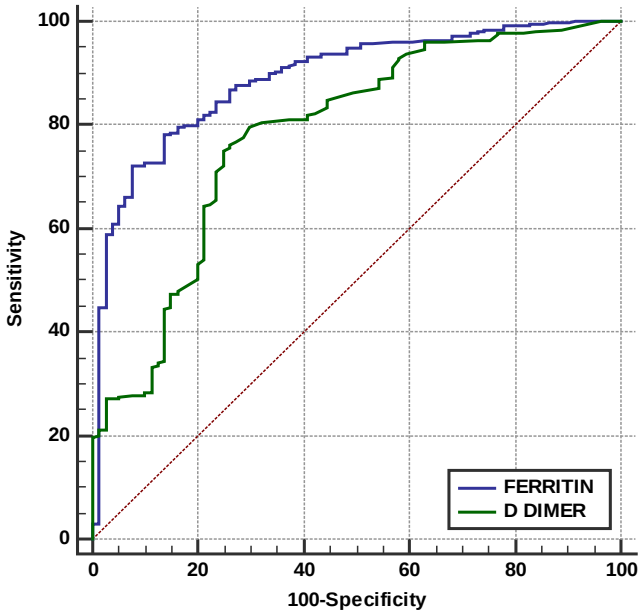

Figure 1. ROC curve for positive CT findings using ferritin and D-Dimer.

Table 3. AUC for ferritin and D-Dimer to predict positive CT findings.

Variable	AUC	95% CI	P-value
Ferritin	0.891	0.860 to 0.917	<0.001
D-Dimer	0.783	0.744 to 0.818	

AUC: Area Under the Curve; CI: Confidence Interval.

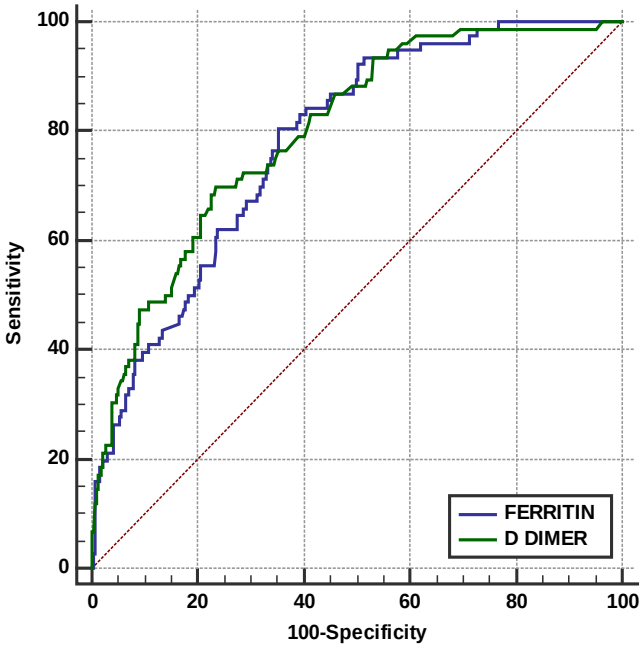

Figure 2. ROC curve for mortality using ferritin and D-Dimer.

Table 4. AUC for ferritin and D-Dimer to predict the occurrence of mortality.

Variable	AUC	95% CI	P-value
Ferritin	0.781	0.742 to 0.817	0.584
D-Dimer	0.799	0.761 to 0.833	

AUC: Area Under the Curve; CI: Confidence Interval.

(95% CI: 64.5% - 84.2%). For mortality, the suggested cutoff point for ferritin using Youden's index is >864.6 ng/mL, which gives a sensitivity of 80.26% (95% CI: 69.5% - 88.5%) and a specificity of 64.83% (95% CI: 60.0% - 69.4%). The suggested cutoff point for D-Dimer using Youden's index is >1.46 mg/L FEU, which gives sensitivity of 65.79% (95% CI: 54.0% - 76.3%), and specificity of 78.23% (95% CI: 74.0% - 82.1%) (Table 5).

4. Discussion

Our study presents information on COVID-19 positive patients admitted to our hospital after being confirmed by a real-time PCR test, with their CT, laboratory findings of ferritin and D-Dimer, together with associated respiratory symptoms and their prognosis of mortality or discharge. We found that higher age, having respiratory symptoms, high ferritin, and high D-Dimer levels at time of patient admission to hospital are significantly associated with positive CT pulmonary findings with high odds ratios (OR) for all. These go in accordance with the, significant findingsof A. Yilmaz *et al*., in their earlier study. However, still the number of studies that describe the association between positive CT findings and blood levels of ferritin and D-Dimer is very limited [11].

By comparing the significance of both laboratory tests in relation to patient prognosis, mortality, and the positive CT findings, while both tests have equal capabilities to detect poor patient outcome with no significant difference and nearly equal AUC in ROC curve analysis, high ferritin levels are more able to predict lung injury and positive CT lung findings with a significant difference between the AUC of both tests and a higher AUC in ferritin than that of D-Dime. The p-value was significant.

Using sensitive and specific cutoff values for both laboratory markers to predict possible lung injury and possible poor patients outcomes may help a lot in triage area, to appropriately identify patients who may need pulmonary CT, and or hospital admission for providing more aggressive treatment and closer monitoring. From ROC curve using Youden's index, we suggested a cutoff value of >336 ng/mL for ferritin as a predictor for positive CT findings, which gives a sensitivity of 78.21% (95% CI: 73.9 - 82.1%), and a specificity of 86.42% (95% CI: 77.0% - 93.0%). The suggested cutoff point for D-Dimer is >0.55 mg/L FEU, which gives a sensitivity of 74.82% (95% CI: 70.3% - 78.9%), and a specificity of 75.31% (95% CI: 64.5% - 84.2%).

For possible poor prognosis and mortality, the suggested cutoff point for

Table 5. Suggested cut off points with corresponding sensitivity and specificity.

	Ferritin			D-Dimer		
	cutoff point ng/mL	Sensitivity (95% CI)	Specificity (95% CI)	Cutoff point (mg/L FEU)	Sensitivity (95% CI)	Specificity (95% CI)
Positive CT findings	>336	78.21% (73.9 - 82.1)	86.42% (77.0 - 93.0)	>0.55	74.82% (70.3 - 78.9)	75.31% (64.5 - 84.2)
Mortality	>864.6	80.26% (69.5 - 88.5)	64.83% (60.0 - 69.4)	>1.46	65.79% (54.0 - 76.3)	78.23% (74.0 - 82.1)

CI: Confidence Interval.

ferritin use is >864.6 ng/mL, which gives a sensitivity of 80.26% (95% CI: 69.5 - 88.5%), and a specificity of 64.83% (95% CI: 60.0 - 69.4%). The suggested cutoff point for D-Dimer is >1.46 mg/L FEU, which gives a sensitivity of 65.79% (95% CI: 54.0 - 76.3%), and a specificity of 78.23% (95% CI: 74.0 - 82.1%).

B.S. Gopala Krishna *et al*. suggest that a significant worsening in C.T. scores is correlated with an increase in D-Dimer levels, which is a signal of lung deterioration and progression. Regarding the poor prognosis, he found that D-Dimer has a higher diagnostic accuracy when compared to ferritin, with an AUC value of 0.598 for ferritin and 0.88 for D-Dimer. The optimal cutoff suggested by them as a poor prognosis predictor was 727 ng/mL for ferritin, with a positive predictive value of 35.5% and a negative predictive value 76.5%. The cutoff for D-Dimer was 2.2 mg/L FEU with a positive predictive value 72.5% and a negative predictive value 88% [12].

However, in another study, Zayed *et al*. showed significant elevation of the ferritin levels in severe COVID-19 patients, with 91% sensitivity and 74 % specificity at a cutoff level of >548.5 ng/mL, AUC value was 0.87 (CI 0.79% - 0.94%), with a significant p-value (<0.001). They suggested using ferritin as an independent predictor of severe COVID-19 [13].

Alvaro *et al*. investigated the significant predictive values of ferritin and D-Dimer to identify patients at risk of developing severe lung injury, Adult Respiratory Distress Syndrome (ARDS). They discovered that there was a significant increase in initial ferritin level at time of hospital admission with an AUC value of 0.86 CI (0.8% - 1%) and a significant p-value (0.001), while D-Dimer level was not initially significant as an indicator of lung injury, but after few days of admission started to be of significant value (p-value < 0.001) [14].

5. Limitations

Being a retrospective study, during the data collection phase, many patients who were eligible for our criteria were excluded due to missing information such as ferritin or D-Dimer results. In addition, time from illness onset to hospital presentation may affect ferritin and D-Dimers values.

6. Conclusion

In this study, we found that laboratory markers such as ferritin and D-Dimer can be an accurate predictor of lung injury in COVID-19 patients and their increased values above our suggested cutoff (>336 ng/mL for ferritin, and >0.55 mg/L FEU for D-Dimer), are correlated with the presence of radiological CT findings not only that but also levels above 864.6 for ferritin and >1.46 mg/L FEU for D-Dimer can predict the poor patient prognosis and possible mortality if patient did not receive enough hospital care and close monitoring in hospital. We thus argue that D-Dimer and ferritin levels measured at the time of admission to the emergency department can be taken into consideration to predict disease severity.

Author's Contribution Statement

All authors contributed to data acquisition. Data analysis, interpretation and manuscript drafting were done by DR. Mona Fathy the corresponding author. Administrative support is done by DR. Ahmed Al Akidi. All authors reviewed and approved the final version of the manuscript.

Data Sharing Statement

Most of the data supporting our findings is contained within the manuscript, and all others, excluding identifying or confidential data, will be shared upon request from the corresponding author.

Ethical Consideration

Participants' anonymity was assured by assigning each participant a code number for the purpose of analysis. There is no need to sign a consent form.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

WHO (World Health Organization).

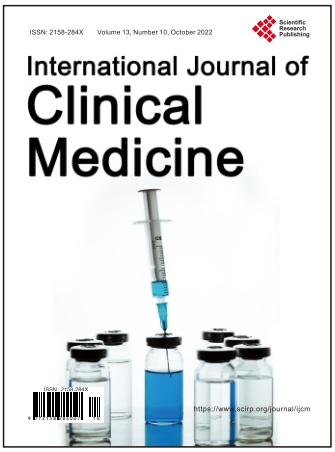
TNFα (Tumor necrosis factor alpha).

PCR (Polymerase chain reaction).

Q1 and Q3 (The first and third quartiles, respectively).

RNA: Ribonucleic acid.

SARS-CoV-2: The severe acute respiratory syndrome-coronavirus 2.



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