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Eksüdatif Plevral Efüzyonda Torakoskopik Biyopsinin Tanısal Rolü ve Uzun Dönem Takip Sonuçları

The Diagnostic Role of Thoracoscopic Biopsy in Exudative Pleural Effusion and Long-Term Follow-Up Results

Hıdır Esme [1]

[1]Sağlık Bilimleri Üniversitesi Konya Şehir Hastanesi Göğüs Cerrahisi Kliniği, Konya, Türkiye

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Özet

Giriş: Eksudatif plevral efüzyonların %20'sinde, tekrarlayan torasentez ve perkutan plevral biyopsiye rağmen tanısı konulamaz. Bu çalışmanın amacı daha az invaziv yöntemlerle tanısı konulamayan eksüdatif PE olan hastalarda yapılan torakoskopik biyopsinin etkinliği ve işlem sonrası uzun dönem takiplerin gözden geçirilmesidir.

Gereç ve Yöntem: Ocak 2016 ile Aralık 2020 tarihleri arasında eksüdatif PE nedeniyle torakoskopik biyopsi uygulanan hastalar geriye dönük incelendi. Postoperatif en az 2 yıl takip edilebilen hastalar çalışmaya dahil edildi. Klinik ve fizik muayene, kan tahlilleri, plevral sıvının biyokimyasal, bakteriyolojik ve sitolojik incelemeleri, radyolojik ve histopatolojik veriler elde edildi.

Bulgular: Hastaların 45'i (%61.6) erkek, 28'i (%38.3) kadındı. Yaş ortalaması 56,5±13,2 idi. Hiçbir hastada intraoperatif komplikasyon gelişmedi. Postoperatif dönemde 7 (%9) hastada komplikasyon gelişti. Üç (%4.1) hastada uzamış hava kaçağı, 2 (%2.7) hastada yara yeri enfeksiyonu ve 2 (%2.7) hastada pnömoni gelişti. Hastaların 21'inde (%28.7) malignite saptanırken 52 (%71.2) hastada benign patolojiler saptandı. Takip sırasında daha önce nonspesifik plörit tanısı alan ve tekrarlayan PE nedeniyle torakoskopik biyopsi yapılan 4 (%5.4) hastadan 2'sinde (%2.7) malign mezotelyoma saptandı.

Tartışma: Sonuç olarak eksudatif PE'nin tanısında torakoskopik biyopsi tanısal değeri yüksek ve komplikasyonları nadir bir yöntemdir. Nonspesifik plevrit sonrası malignite gelişimi genellikle 1 yıl içerisinde olmakla birlikte nadiren 2 yıl içinde de gelişebilir. Bu nedenle nonspesifik plevrit sonrası takip süresinin 2 yıl olması gerektiği kanaatindeyiz.

Anahtar Kelimeler: Eksüda, Torakoskopi, Uzun dönem takip.

Abstract

Aim: In 20% of exudative pleural effusions, the diagnosis cannot be established despite repeated thoracentesis and percutaneous pleural biopsy. The aim of this study was to review the effectiveness of thoracoscopic biopsy performed in patients with exudative PE that could not be diagnosed with less invasive methods and their long-term follow-up after the procedure.

Materials and Methods: Patients who underwent thoracoscopic biopsy for exudative PE between January 2016 and December 2020 were retrospectively analyzed. Patients who were followed up for at least 2 years postoperatively were included in the study. Clinical and physical examination, blood tests, biochemical, bacteriological and cytological examinations of pleural fluid, radiological and histopathological data were obtained.

Results: Forty five (61.6%) of the patients were male and 28 (38.3%) were female. The mean age was 56.5±13.2 years. No intraoperative complications developed in any patient. Complications developed in 7 (9%) patients in the postoperative period. Prolonged air leakage developed in three (4.1%), wound infection in 2 (2.7%), and pneumonia in 2 (2.7%) patients. While malignancy was detected in 21 (28.7%) patients, benign pathologies were detected in 52 (71.2%) patients. During follow-up, malign mesothelioma was detected in 2 (2.7%) of 4 (5.4%) patients who were previously diagnosed with nonspecific pleuritis and underwent thoracoscopic biopsy due to recurrent PE.

Conclusion: Thoracoscopic biopsy is a method with high diagnostic value and rare complications in the diagnosis of exudative PE. Although the development of malignancy after nonspecific pleuritis is usually within 1 year, it can also develop within 2 years. Therefore, we believe that the follow-up period after nonspecific pleuritis should be 2 years.

Keywords: Exudate, Thoracoscopy, Long-term follow-up.

***Sorumlu Yazar / Corresponding Author:** Hıdır Esme, Sağlık Bilimleri Üniversitesi Konya Şehir Hastanesi Göğüs Cerrahisi Kliniği, Konya, Türkiye **E-mail**: drhesme@hotmail.com

GİRİŞ

Plevral efüzyon (PE) plevral boşlukta anormal sıvı birikimidir (1). PE kanser, enfeksiyon, inflamasyon veya kalp, karaciğer ve böbrek gibi organların işlev bozukluğunun neden olduğu yaygın bir klinik semptomdur (2). Hastalarda görülen temel semptom nefes darlığıdır. Önceden, plevral efüzyon tanısı esas olarak klinik öykü, fizik muayene, görüntüleme teknikleri, torasentez ve perkütan plevral biyopsi ile konulmaktaydı. Bununla birlikte, bu yöntemlerin tanısal veriminin düşük olduğu ve plevral efüzyonun geç tanısının, belirgin şekilde daha yüksek morbidite ve mortalite ile ilişkili olduğu bilinmektedir. Buna karşın etkin, güvenli, basit ve uygun maliyetli, minimal invaziv bir prosedür olan torakoskopik biyopsi, plevral efüzyon ve plevral hastalıkların tanı ve tedavisinde belirgin avantajlara sahiptir (3). Bu nedenlerle torakoskopik biyopsi şu anda plevral efüzyon tanısında altın standarttır (4). Torakoskopik biyopsinin ana avantajı, makroskopik olarak şüpheli tüm plevral lezyonların incelenebilmesidir. Torakoskopinin tanısal veriminin %93'e kadar çıktığı bildirilmiştir (5). Torakoskopi ile plörit tanısı konulduğu halde takiplerde malignitenin ortaya çıkabildiği de bilinen bir gerçektir. Torakoskopik biyopsi sonrası uzun dönem takipleri inceleyen az sayıda çalışma vardır. Bu çalışmada daha az invaziv yöntemlerle tanısı konulamayan eksüdatif PE olan hastalarda yapılan torakoskopik biyopsinin etkinliği ve işlem sonrası uzun dönem takiplerinin gözden geçirilmesi amaçlanmıştır.

GEREÇ ve YÖNTEM

Bu retrospektif çalışmaya Ocak 2016 ile Aralık 2020 tarihleri arasında tanı amaçlı, eksüdatif PE nedeniyle torakoskopik biyopsi uygulanan 18 yaşından büyük ve postoperatif en az 2 yıl takip edilebilen 73 hasta dahil edildi. Çalışma, Helsinki Deklarasyonu 2008 Prensipleri'ne uygun olarak yapıldı. Çalışmaya Sağlık Bilimleri Üniversitesi Konya Şehir Hastanesi Eğitim Planlama Kurulu tarafından 02.03.2023 tarih ve 34028103-799 kayıt no.lu karar ile onay verildi. Eksüdatif PE nedeniyle torakoskopik biyopsi uygulanan tüm hastaların bilgileri dosya arşivi ve otomasyon sisteminden retrospektif olarak incelendi. Klinik ve fizik muayene, kan tahlilleri, plevral sıvının biyokimyasal, bakteriyolojik ve sitolojik incelemeleri ile birlikte

radyolojik ve histopatolojik veriler elde edildi. Torasentez, perkutan transtorasik plevra biyopsisi veya bronkoskopi ile tanı konulan eksüdatif PE'li hastalar çalışmaya dahil edilmedi.

VATS (video-assisted thoracoscopic surgery) biyopsi işlemi tüm hastalara genel anestezi altında, çift lümenli endotrakeal tüp yerleştirilerek, tek akciğer ventilasyonu uygulanarak yapıldı. İşlem uniportal olarak uygulandı. Plevradan histopatolojik inceleme için en az 4 şüpheli alandan biyopsi alındı. Paryetal plevranın makroskopik olarak normal olduğu hastalarda biyopsiler posterior kostodiyafragmatik alandaki paryetal plevradan alındı. Histopatolojik inceleme ile birlikte tüm hastalarda tüberküloz kültürü incelemesi için de materyal gönderildi. Torakoskopik biyopsi sırasında malignite şüphesi yüksek hastalarda frozen section yapıldı. Malign ve akciğer rezesiyonu yapılamayacak olan hastalarda terapötik veya palyatif amaçlı dekortikasyon ve talk plörodezis yapıldı. Erken ve geç komplikasyonlar hastane kayıtlarından not edildi.

Biyopsi materyallerinin histopatolojik incelemelerinde malign lezyonlar hücre tipine göre alt sınıflara ayrıldı. Periyodik asit-Schiff (PAS) ve Ehrlich-Ziehl-Neelsen (EZN) boyaları, mantar ve aside dirençli bakteriyel enfeksiyonların varlığını belirlemek için kullanıldı. Histopatolojik incelemede malign infiltrasyon yokluğunda fibrozis, plevral kalınlaşma ve benign reaktif değişiklik bulguları olan kronik plörezili hastalar nonspesifik plörezi olarak tanımlandı.

BULGULAR

Ocak 2016 ile Aralık 2020 tarihleri arasında 73 hastaya eksüdatif PE nedeniyle torakoskopik biyopsi yapıldı. Hastaların 45'i (%61,6) erkek, 28'i (%38,3) kadındı. Genel yaş ortalaması 56,5±13,2 idi. Hastaların 41'inde (%56,1) sigara, 12'sinde (%16,4) asbest maruziyeti, 5'inde (%6,8) malignite ve 3'ünde (%4,1) tüberküloz hikayesi vardı.

Hiçbir hastada intraoperatif komplikasyon gelişmedi. Postoperatif dönemde 7 (%9) hastada komplikasyon gelişti. Üç (%4,1) hastada uzamış hava kaçağı, 2 (%2,7) hastada yara yeri enfeksiyonu ve 2 (%2,7) hastada ise pnömoni gelişti. Postoperatif erken dönem ölüm olmadı. Hastaların 21'inde (%28,7) malignite saptanırken 52 (%71,2) hastada benign patolojiler saptandı. Malignite grubundaki hastaların histopatolojik incelemesinde 7 (%9,5) hastada mezotelyoma, 6 (%8,2) hastada primer akciğer kanserine bağlı plevra metastazı, 5 (%6,7) hastada akciğer dışı organ kanseri metastazı ve 3 (%4,1) hastada ise lenfoma saptandı. Benign patoloji saptanan hastaların 44'ünde (%60,2) kronik nonspesifik plevrit, 6'sında (%8,2)

kazeifikasyon nekrozu gösteren granülamatöz hastalık, 2'sinde (%2,7) ise nonkazeifiye granülomatoz iltihap saptandı.

Hastaların hastane yatış süresi 4,3±2,4 gün idi. Taburculuk sonrası ortalama takip süresi 28,2±16,1 (min-max: 25-35) ay idi. Takip sırasında daha önce nonspesifik plörit tanısı alan ve tekrarlayan PE nedeniyle torakoskopik biyopsi yapılan 4 (%5,4) hastadan 2'sinde (%2,7) mezotelyoma saptandı (Tablo 1). Diğer benign histopatolojik tanıya sahip hastalarda PE tekrar etmedi.

Tablo 1: Hastaların torakoskopik biyopsi sonuçları ve klinik bulguları

Hasta verileri	**n (%)**
Torakoskopik biyopsi sonucu malign	21 (%28,7)
Mezotelyoma	7 (%9,5)
Akciğer Carsinom metastazı	6 (%8,2)
Akciğer dışı malignite metastazı	5 (%6,7)
Lenfoma	3 (%4,1)
Torakoskopik biyopsi sonucu benign	52 (%71,2)
Nonspesifik plevrit	44 (%60,2)
Kazeifikasyon nekrozu	6 (%8,2)
Nonkazeifiye granulomatöz hastalık	2 (%2,7)
Postoperatif komplikasyon	7 (%9,5)
Uzamış hava kaçağı	3 (%4,1)
Pnömoni	2 (%2,7)
Yara yeri enfeksiyonu	2 (%2,7)
Hastane yatış süresi (Gün)	4,3 ± 2,4
Takip süresi (Ay)	28,2 ± 16,1 (min-max: 25-35)
Takip sürecinde ortaya çıkan malignite	
Mezotelyoma	2 (%2,7)

TARTIŞMA

Nedeni bilinmeyen eksüdatif PE, önemli sonuçları olan ve sık görülen bir sorun olmaya devam etmektedir. PE genellikle intratorasik bir hastalığın işareti olmakla birlikte daha az sıklıkla ekstratorasik veya sistemik bir hastalığın belirtisi de olabilir (6,7). PE tanısında ilk basamak torasentez ve kapalı plevra biyopsisi yapılmasıdır. Plevral efüzyonu bulunan hastalara yapılan torasentez ve kapalı plevra biyopsisi ile hastaların %30 ile 80 arasındaki oranlarda tanı konulamamaktadır (4). Bu nedenle tanısı konulamayan eksüdatif PE'de torakoskopik biyopsi yaygın olarak kullanılmaktadır. Eksüdatif PE olan hastalarda tanıya yönelik yapılan çok

sayıdaki çalışmada genellikle etiyolojide malign nedenlerin diğer nedenlerden daha fazla yer aldığı gözlenmektedir (9,10). Ancak çalışmamızda literatürün aksine benign nedenler daha fazla bulundu. Hastaların %29'unda malignite saptanırken %71'inde benign patolojiler saptandı. En sık sebep kronik nonspesifik plevrit idi.

Çalışmalar torakoskopik biyopsinin diğer yöntemlerle tanısı konamayan eksüdatif PE için oldukça duyarlı ve güvenilir bir yöntem olduğunu göstermiştir. Torakoskopik biyopsinin PE'de %95'in üzerinde bir tanı oranı elde ettiği bildirilmiştir (8,11-13). Torakoskopi sırasında tüm plevral boşluğun incelenebilmesi ve çok sayıda doku örneklemesine izin verme potansiyeli, bu prosedürün tanısal başarısı için önemli avantajlardır (14,15). Bununla birlikte, eksüdatif PE'li bazı hastalara nonspesifik akut veya kronik plörit teşhisi konulmakta ve torakoskopik biyopsiden sonra bile etiyoloji belirsizliğini korumaktadır (9,16-18). Bu tür vakalar genellikle "nonspesifik plörit", "fibrinöz plörit" veya "idyopatik plörit" olarak rapor edilmektedir. Nonspesifik plörit tanısı, örnekleme hatasından kaynaklanan yanlış negatif sonuçlar göz önünde bulundurulduğunda klinisyenler için zor bir durumdur. Yayınlanmış veriler, bu hastaların %5 ile %25,5'ine daha sonra plevral malignite teşhisi konulacağını göstermektedir ve bu maligniteler içinde en yaygın olarak görüleni %2,5 ile %15,8 sıklıkta mezotelyomadır (9, 17-19). Çalışmamızda nonspesifik plöriti olan 2 (%1,6) hastada malignite saptandı. Kalan hastalarda iyi huylu bir seyir vardı.

Spesifik olmayan plöritli hastaların uzun vadeli sonuçları hakkında sınırlı veri olduğundan, standartlaştırılmış takip kriterleri ve süre belirlenmemiştir. Optimal takip süresi açısından literatür kapsamında bir fikir birliği yoktur. Birçok çalışmada ortalama takip süresi 21,3 ile 62 ay arasında değişir (9,17-21). Yang ve ark. nonspesifik plöritli 52 hastanın 8'inin ilk biyopsiden sonraki 12 ay içinde malignite tanısı aldığını bildirmiştir. Ortalama takip süresi 35,5 ay olan hastalarda malign mezotelyoma tanısı için geçen maksimum süre 10 ay idi. Bu çalışmada, 12 aylık klinik takibin, maligniteleri çoğunu saptamak için muhtemelen yeterli olduğu sonucuna varılmıştır (21).

Başka bir çalışmada, nonspesifik plöritli hastalarda malignitenin büyük olasılıkla ilk plevral biyopsiden sonraki 1 yıl içinde olacağını, ancak daha uzun sürelerin de mümkün olduğunu bildirmişlerdir (17). Deschuyteneer ve arkadaşları nonspesifik plöritis sonrası malign plöritis saptanan hastaların genellikle 1 yıl içerisinde ortaya çıktığını ancak nadiren bu sürenin 2 yıl olabileceği sonucuna varmışlardır (22). Çalışmamızda ortalama takip süresi 28,2±16,1 (25-35) ay idi. 24 aydan uzun süre izlenen nonspesifik plörezili hastaların oranı %36 idi ve hiçbirinde malignite gelişmedi. Tüm hastalarımız değerlendirildiğinde, ilk biyopsiden sonraki 9 ve 15 ay

içinde 2 olguda malign mezotelyoma gelişti. Bu bulgular ışığında, 12 aylık takip süresinin yeterli olmayacağını düşünüyoruz.

SONUÇ

Nedeni ortaya konamamış eksüdatif PE'nin tanısında torakoskopik biyopsi tanısal değeri yüksek ve komplikasyonları nadir olan bir yöntemdir. Nonspesifik plevrit sonrası malignite gelişimi genellikle 1 yıl içerisinde olmakla birlikte nadiren 2 yıl içinde de gelişebilir. Bu nedenlerle, nonspesifik plevrit sonrası takip süresinin 2 yıl olması gerektiği kanaatindeyiz.

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The Effect of Inhaler Treatment with a Therapeutic Nebulizer Designed with 3D Printing Technology on Children's Psychosocial Symptoms

3D Baskı Teknolojisi ile Tasarlanan Terapötik Nebülizatör Cihazı ile Yapılan İnhaler Tedavinin Çocukların Psikososyal Semptomlarına Etkisi

Nurten ARSLAN[1*], Meltem KÜRTÜNCÜ[1]

[1]Department of Pediatric Nursing, Faculty of Health Sciences, Zonguldak Bülent Ecevit University, Zonguldak, Turkey

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Abstract

Objective: This research was carried to minimize psychosocial symptoms such as fear, anxiety and crying by hospitalized children undergoing inhaler treatment with a nebulizer developed with three-dimensional printing technology and to examine the effect of this method on parental satisfaction.

Methods: The study is of experimental design. 44 children between the ages of 2-7 receiving inhaler therapy with a nebulizer and their parents were recruited into the experimental and control groups. The researchers collected the data with "Scale for Identifying Psychosocial Symptoms in Hospitalized Children" and the "PedsQL Healthcare Satisfaction Scale."

Results: It was noted that 45 of the children included in the study were boys, 43 were between the ages of 2-3, 75 were receiving treatment for bronchitis, 50 had previously been hospitalized for the same sickness and 68 had previously received inhaler therapy. It was observed that among the parents, 83 were mothers, 39 had a primary school education or less, and 76 were unemployed. In the experimental group, 81.8 percent of the children being treated with a 3D therapeutic device who had previously received treatment in the same way were not fearful, while 27.3 percent of those being treated with a standard type of nebulizer in the control group were unafraid ($X^2 = 24.246$; $p < 0.001$). While those who were not crying at the time of their therapy made up 71.9% in the experimental group, this rate was 36.4 percent in the control group ($X^2 = 28.686$; $p < 0.001$). The difference between the groups was significant ($p < 0.001$). The t-test performed to compare the pre- and posttests in the experimental group revealed a significant difference of $p = 0.002$. In the control group, where $p = 0.051$, no significant difference was seen. In the comparisons of the Healthcare Satisfaction Scale (PedsQL), the difference between the mean scores of the experimental and control groups was found to be significant ($p = 0.026$).

Conclusions: It was concluded that inhaler therapy administered with a therapeutic nebulizer designed with three-dimensional printing technology reduced psychosocial symptoms and positively impacted parental satisfaction. This study highlights that was carried out with the aim of minimizing psychosocial symptoms by hospitalized children undergoing inhaler treatment with a nebulizer developed with three-dimensional printing technology.

Keywords: Child, Inhalers, Hospitalization, Psychosocial Symptom, Three-Dimensional Printing, Therapeutics.

Özet

Amaç: Bu çalışma; 3D baskı teknolojisi ile geliştirilen nebülizatör cihazı ile yapılan inhaler tedavinin hastanede yatan çocuklarda tedaviye ilişkin korku, anksiyete, ağlama gibi psikososyal semptomları en aza indirmek ve ebeveyn memnuniyetine etkisini incelemek amacıyla gerçekleştirildi.

Yöntem: Araştırma deneysel tasarımdadır. Deney ve kontrol gruplarına yaşları 2-7 arasında nebülizatörle inhaler tedavisi gören 44 çocuk ve ebeveynleri alındı. Veriler araştırmacı tarafından hazırlanmış 'Kişisel Bilgi Formu ile 'Hastanede Yatan Çocuklar İçin Psikososyal Semptomları Tanılama Ölçeği' ve 'Pedsql Sağlık Bakımı Memnuniyet Ölçeği' ile toplandı.

Bulgular: Çalışmaya dahil edilen çocukların 45'inin erkek, 43'ünün 2-3 yaş, 75'inin bronşit tedavisi aldığı, 50'sinin daha önce aynı hastalık nedeniyle hastaneye yattığı ve 68'inin daha önceden inhaler tedavi aldığı görüldü. Ebeveynlerin 83'ünün anne, 39'unun eğitim durumunun ilkokul ve altı eğitim seviyesinde, 76'sının çalışmadığı görüldü. Deney grubunda 3D terapötik cihazla önceden tedavi alanlarda tedavi esnasında korkmayanların yüzdesi 81,8 iken kontrol grubunda standart tip nebülizatör ile tedavi alanlarda 27,3 ($X^2 =$

24,246; p <0,001); deney grubunda şu an ağlamayanların yüzdesi 71,9 iken kontrol grubunda 36,4 (X^2 = 28,686; p <0,001) olup gruplar arasındaki farklılık anlamlı görüldü (p <0,001). Deney grubu ön test-son test karşılaştırmalarında yapılan t testi sonucu p=0,002 olup anlamlı farklılık saptandı. Kontrol grubunda ise p=0,051 olup anlamlı farklılık saptanmadı. Sağlık Bakım Memnuniyet Ölçeği (PedsQL) karşılaştırmalarında deney ve kontrol grubu puan ortalamaları arasındaki fark anlamlı bulundu (p=0,026).
Sonuç: 3D teknolojisi ile tasarlanan terapötik nebülizatör cihazı ile yapılan inhaler tedavinin psikososyal semptomları azalttığı ve ebeveyn memnuniyetine etki ettiği sonucuna varıldı. 3D teknolojisi ile tasarlanan nebülizatör cihazı ile yapılan inhaler tedavisi çocuklarda psikososyal semptomları azaltmak için hem klinikte hem de acil servislerde uygulanabilir.

Anahtar Kelimeler: Çocuk, İnhaler, Hastaneye Yatış, Psikososyal Semptom, 3D Baskı Teknolojisi, Tedavi.

***Sorumlu Yazar / Corresponding Author:** Nurten Arslan, Department of Pediatric Nursing, Faculty of Health Sciences, Zonguldak Bülent Ecevit University, Zonguldak, Turkey **E-mail**: anurtenarslan@gmail.com

INTRODUCTION

Aerosol therapy is the typical treatment modality for respiratory infections in children. Its main purpose is to humidify the respiratory tract, dilute sputum and discharge it smoothly, and achieve treatment of the disease (1-3). Pediatric health management is a strictly professional challenge. Establishing good interaction with children is a priority problem and a difficult task for nurses helping children receive such treatment during hospitalization (4,5).

The nebulizer devices frequently used in pediatric treatment operate at high pitch and are generally of the appearance and type that actually diminish a child's treatment compliance. Most children exhibit signs of fear, are resistant and even unwilling to use the inhaler, believing that the disease cannot be treated, all of which leads to incredible frustration for both family and nurses (2,6). A prolonged hospital stay not only affects the timeliness of treatment, but also impacts the disease recovery process (4). Any crisis that a child may experience concerning an illness or as a result of the hospital stay may cause developmental trauma and leave a lasting scar (7,8). Nurses need to engage in nursing initiatives that will serve to eliminate psychosocial issues and increase the capacity of the hospitalized child and the family to adapt (2,6,7).

The nebulizer devices frequently used in pediatric treatment operate at high pitch and are generally of the appearance and type that actually diminish a child's treatment compliance (9,10). The issue of a child's anxiety over the device's arrival is commonly encountered. Some studies have pointed to a lessening of treatment efficacy due the fear and anxiety children experience in response to the appearance, emitted sounds and noises of hospital nebulizers and cold steam humidifiers (4,6). Nurses should use therapeutic approaches in their effort to

increase a child's compliance, clearly identifying and eliminating the negative impact that medical devices may have on children (2,6).

The aim of this study was to reduce the psychosocial symptoms of children receiving inhaler therapy with a nebulizer developed by the researchers with 3D printing technology (3D-TND-3D Therapeutic Nebulizing Device) and at the same time, to increase parental satisfaction. Three-dimensional (3D) printing technology is a rapidly developing technique that has been used in various fields today. 3D printing is a printing process which enables a hard copy printout to be obtained from any three-dimensional model. The capability of this technique to reduce both production costs and the need for raw materials and produce an end-product from only the amount of raw materials that is needed for the project differentiates this technology from traditional processes (2,3). The need for visual materials has also grown in nursing care services, and consequently, the use of visual aids has become more widespread (11,12).

Integrating updated technology such as 3D printing into the sphere of healthcare has made a higher quality of healthcare services available to patients and their caregivers (2). As a result, nurses who aim to provide their patients with holistic care can now more minimize any psychosocial symptoms or complications they may observe.

Aim

This research was carried out to of minimise psychosocial symptoms such as fear, anxiety and crying behavior displayed by pediatric in patients undergoing inhaler treatment with a nebulizer developed with 3D printing technology (3D-TND), and to examine the effect of this method on parental satisfaction.

METHODS

Participants were asked to sign a Participant Informed Consent Form in the conduct of the study. The researcher explained to the 88 parents taken into the 3D-TND and SND (Standard Nebulizer Device) groups about the purpose of the study and what was expected of them, pointing out that participation was based on volunteerism and that they could withdraw from the study at any time they wished to do so. Permission for the conduct of the study was obtained from the Clinical Studies Ethics Committee of a university date and no: (2018-172-01/08) and from the administration of the hospital in which the research was being carried out.

3D-TND: It is a device that looks like a turtle nebulizer device designed and produced by researchers using a 3D printer to be used in device research. Before the device was produced,

researcher N.A received training on three-dimensional printers and designed the device. In the printing, attention was paid to the use of raw materials that would harm children's health and a therapeutic appearance that would not cause fear and anxiety in the people in the appearance. It is a prototype device produced for device research. Division of the device regarding technical information when necessary. Please see Fig. 1.

1.1.Place and time of the study

The research was conducted as an experimental, analytical study. The study was carried out in one of the two hospitals in the city of Turkey with a pediatric clinic. The researchers determined which hospital the study would be conducted in by means of a lottery draw. The institution where the study was carried out had a specialized pediatric clinic with a 30-bed capacity. The study took place over the period November 15, 2018 - May 15, 2019.

1.2.Participants

It was noted that 403 pediatric inpatients receiving inhaler treatment who had been hospitalized for upper respiratory tract conditions in this clinic over the past 6-month period. Among these children, 246 between the ages of 2-7 constituted the universe of the study. A sample size calculation for a known population made from this universe at a 95% confidence interval and 5% significance determined that the sample size would be 120. Ninety-six children of those in the sample agreeing to be included in the research at the time the study was being conducted were included. Power analysis was used for sample calculation. In case the effect width value was 0.70 at a 5% margin of error and 81.23% power level, the total number of individuals was determined as 88, including 44 patients for two repeated measurements in the groups (13). The random number table was used to determine the 3D-TND and SND groups in the study. The children hospitalized in the clinic with the mentioned diagnoses were assigned to the 3D-TND and SND groups in the order of their date of admittance as from the start of the study. For example, while one pediatric patient was 5^{th} to be admitted for treatment and assigned to the 3D-TND group, the child 11^{th} to be admitted was assigned to the SND group. This method was chosen to avoid bias. The study was completed with 88 pediatric patients are distributed to semi-half groups.

1.3.Instruments

Personal information form

This form consists of information on each child, namely the variables of gender, age, medical diagnosis, duration of hospitalization, previous hospitalizations, how many times the child has

been hospitalized, if ever, whether or not the child had previously received steam/nebulizer therapy.

Scale for Identifying Psychosocial Symptoms in Hospitalized Children (SIPS)

Üstün & Kelleci (2012) produced the validity and reliability study of this scale for the purpose of creating an instrument that would provide the means to identify the psychosocial symptoms of pediatric inpatients. The scale is a Likert-type of instrument with 24 items. Higher scores on the scale indicate that the hospitalized child has psychosocial issues (14). In this study, Cronbach's alpha value was calculated to be α=0.947.

The PedsQL Healthcare Satisfaction Scale

The scale was developed by Varni (Varni, 2005) in 1999 (15). The Turkish translation, validity and reliability testing of the scale were performed by Ulus (16). A total score indicates the level at which satisfaction has been achieved. In this study, Cronbach's alpha value was calculated to be α=0.806.

Intervention

- The data collection forms were filled out with either one of the parents of the hospitalized children in a face-to-face interview.
- The Personal Information Form comprising the descriptive characteristics of the children and their parents was used in the data collection.
- The SIPS in Hospitalized Children was used to identify the psychosocial symptoms of the hospitalized children.
- The PedsQL Scale was used to measure the parents' satisfaction with the medical services provided as well as their psychosocial satisfaction
- The inhaler therapy using the 3D-TND developed with 3D printing technology was applied from the first stage of the child's admittance into the hospital until discharge.
- The researcher responsible for data collection conducted the collection of data and the interviews with the parents.

1.4. Statistical analysis

The IBM SPSS 22.0 program was used for the statistical analysis. Descriptive statistical methods were used in the analysis of the study data. Normality was investigated with Normality Tests with Plots. The nonparametric test Mann Whitney U test and the Wilcoxon paired sample test were then employed.

RESULTS

The study results were examined in three contexts–sociodemographic findings, findings related to psychosocial symptoms and by making scale comparisons.

Findings concerning sociodemographic characteristics

Of the children in the 3D-TND group included in the study, 26 were boys and 26 were preschool children. It was observed that 42 of the parents in the 3D-TND group were mothers, 21 were under the age of 30, 36 were unemployed, 15 were in primary school, 16 were secondary school educated, 35 had an income equal to their expenses, and 21 lived in the city center. Of the children in the SND group included in the study, 25 were girls and 30 were preschool children. It was observed that 41 of the parents in the SND group were mothers, 23 were under the age of 30, 40 were unemployed, 14 were primary school, 13 were secondary school educated, 31 had an income equal to their expenses, and 22 lived in the city center.

Findings concerning psychosocial symptoms

Of the children in the 3D-TND study group, 59.1% had been previously hospitalized, 86.4% had once received inpatient nebulizer therapy. Among the children once receiving nebulizer therapy, 68.2% cried, 59.1% were fearful, 59.1% tried to avoid the treatment. In the 3D-TND group, it was found that 81.8% of the children receiving 3D-TND nebulizer treatment were not fearful and 93.2% did not exhibit crying symptoms.

Of the children in the SND group, 54.5% had been previously hospitalized, 68.2% had received inpatient nebulizer therapy in their previous hospitalization. Among the children previously receiving nebulizer treatment, 52.3% cried, 52.3% were fearful, 4.9% tried to avoid the treatment. Among their parents, 43.2% thought that they had not received effective nebulizer treatment. In the SND group, it was found that 27.3% of the children receiving SND nebulizer therapy were not fearful and 36.4% did not exhibit crying symptoms. The distribution of diagnostic and psychosocial symptom findings among the children in the 3D-TND and SND groups can be seen in Table 1.

Table 1. Distribution of diagnostic and psychosocial symptom findings among the children

Symptoms by admittance status		3D-TND (n = 44)		SND (n = 44)	
		Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Diagnosis	Bronchitis	41	93,2	34	77,3
	Asthma	2	4,5	7	15,9
	Pneumonia	1	2,3	3	6,8
Hospitalized previously?	Yes	26	59,1	24	54,5
	No	18	4,9	20	45,5
Previously received nebulizer treatment?	Yes	38	86,4	30	68,2
	No	6	13,6	14	31,8
Cried in previous hospitalization?	Yes	30	68,2	23	52,3
	No	9	2,5	8	18,2
	Not received treatment	5	11,4	13	29,5
Was fearful in previous hospitalization?	Yes	26	59,1	23	52,3
	No	13	29,5	8	18,2
	Not received treatment	5	11,4	13	29,5
Previously avoided treatment?	Yes	26	59,1	18	4,9
	No	13	29,5	12	27,3
	Not received treatment	5	11,4	14	31,8
Believing previous treatment was effective	Yes	14	31,8	11	25,0
	No	26	59,1	19	43,2
	Not received treatment	4	9,1	14	31,8
Feeling fearful right now	Yes	8	18,2	32	72,7
	No	36	81,8	12	27,3
Crying right now	Yes	3	6,8	28	63,6
	No	41	93,2	16	36,4
Total		44	100	44	100

The chi-square test was used in the comparison of the psychosocial symptoms of the children in the 3D-TND and SND groups. In the 3D-TND group, 76.9% of the children who had been fearful while being treated with SND were not afraid in their 3D-TND treatment and 92.3% did not cry ($p>0.05$). Of the children who had called during their SND treatment, 8.0% were not fearful during their therapy with 3D-TND and 93.3% did not cry ($p>0.05$) (Table 2.a).

Table 2.a. Comparison of psychosocial symptoms among children in the 3D-TND group who had previously received SND and were now receiving 3D-TND nebulizer treatment

			Fearful now with 3D-TND		
			Yes	No	**Total**
Fearful with SND (before)	Yes	Frequency	6	20	26
		% among those fearful before	23,1	76,9	100
		% among those fearful now	75,0	55,6	59,1
	No	Frequency	1	12	13
		% among those fearful before	7,7	92,3	100
		% among those fearful now	12,5	33,3	29,5
	Not received treatment	Frequency	1	4	5
		% among those fearful before	2,0	8,0	100
		% among those fearful now	12,5	11,1	11,4

Chi-Square = 1,430 and p = ,527

			Crying now with 3D-TND		
			Yes	No	**Total**
Fearful with SND (before)	Yes	Frequency	2	24	26
		% among those fearful before	7,7	92,3	10,0
		% among those crying now	66,7	58,5	59,1
	No	Frequency	0	13	13
		% among those fearful before	0	100	100
		% among those crying now	0	31,7	29,5
	Not received treatment	Frequency	1	4	5
		% among those fearful before	2,0	8,0	10,0
		% among those fearful now	33,3	9,8	11,4

Chi-Square = 2,384 and p = ,204

			Fearful now with 3D-TND		
			Yes	No	Total
Crying with SND (before)	Yes	Frequency	2	24	30
		% among those crying before	2,0	8,0	100
		% among those fearful now	75,0	66,7	68,2
	No	Frequency	1	8	9
		% among those crying before	11,1	88,9	10,0
		% among those fearful now	12,5	22,2	2,5
	Not received treatment	Frequency	1	4	5
		% among those crying before	2,0	8,0	10,0
		% among those fearful now	12,5	11,1	11,4

Chi-Square = ,496 and p = ,855

			Crying now with 3D-TND		
			Yes	No	Total
Crying with SND (before)	Yes	Frequency	2	28	30
		% among those crying before	6,7	93,3	10,0
		% among those crying now	66,7	68,3	68,2
	No	Frequency	0	9	9
		% among those crying before	0	100	100
		% among those crying now	0	22	2,5
	Not received treatment	Frequency	1	4	5
		% among those crying before	20	80	100
		% among those fearful now	33,3	9,8	11,4

Chi-Square = 2,026 and p = ,398

In the SND group, 82.6% of the children who had been once fearful during their therapy with SND were fearful during their present therapy with SND and it was seen that 73.9% cried ($p<0.05$). Among the children who had previously called in their therapy with SND, 82.6% were fearful during their present therapy with SND and it was seen that 73.9% called ($p<0.05$) (Table 2.b).

Table 2.b Comparison of psychosocial symptoms among children in the SND group who had previously received SND and were now again receiving SND nebulizer therapy

			Fearful of SND treatment now		
			Yes	No	**Total**
Fearful with SND (before)	Yes	Frequency	19	4	23
		% among those fearful before	82,6	17,4	100
		% among those fearful before	59,4	33,3	52,3
	No	Frequency	3	5	8
		% among those fearful before	37,5	62,5	100
		% among those fearful before	9,4	41,7	18,2
	Not received	Frequency	10	3	13
		% among those fearful before	76,9	23,1	100
		% among those fearful now	31,3	25,0	29,5

Chi-Square = 5,568 and p = ,052

			Crying in SND treatment now		
			Yes	No	**Total**
Yes		Frequency	17	6	23
		% among those fearful before	73,9	26,1	100
		% among those crying now	6,7	37,5	52,3
No		Frequency	1	7	8
		% among those fearful before	12,5	87,5	100
		% among those crying now	3,6	43,8	18,2
Not received		Frequency	10	3	13
		% among those fearful before	76,9	23,1	100
		% among those fearful now	35,7	18,8	29,5

Chi-Square = 1,251 and p = ,005

			Fearful of SND treatment now		
			Yes	No	Total
Crying with SND (before)	Yes	Frequency	19	4	23
		% among those crying crying before	82,6	17,4	100
		% among those fearful now	59,4	33,3	52,3
	No	Frequency	3	5	8
		% among those crying before	37,5	62,5	100
		% among those fearful now	9,4	41,7	18,2
	Not received	Frequency	10	3	13
		% among those crying before	76,9	23,1	100
		% among those fearful before	31,3	25,0	29,5

Chi-Square = ,496 and p = ,855

			Crying in SND treatment now		
			Yes	No	Total
Yes		Frequency	17	6	23
		% among those crying before	73,9	26,1	100
		% among those crying now	6,7	37,5	52,3
No		Frequency	1	7	8
		% among those crying before	12,5	87,5	100
		% among those crying now	3,6	43,8	18,2
Not received treatment		Frequency	10	3	13
		% among those crying before	76,9	23,1	100
		% among those fearful now	35,7	18,8	29,5

Chi-Square = 2,026 and p = ,398

Results of scale comparisons

The results of the comparisons of the pretest-posttest values of the scales in the 3D-TND and SND groups using the Wilcoxon test are given in Table 3. Accordingly, the participants in the 3D-TND group displayed a significant difference between the results of the *SIPS pre- and posttests* (p=0.004). This indicated that psychosocial symptoms had diminished. The

participants in the SND group displayed no significant difference between the results of the SIPS pre- and posttests (p=0.657).

Table 3. Comparison of pretest-posttest scale results in the 3D-TND and SND groups

		3D-TND group			SND group		
Scales		Mean ± SD	Min	Max	Mean ± SD	Min	Max
PedsQ Healthcare Satisfaction Scale	Receiving information (pretest)	72,22 ± 23,40	15,00	100	69,86 ± 18,69	2,00	100
	Receiving Information (posttest)	82,74 ± 17,51	25,00	100	69,66 ± 17,76	3,00	100
		Z = -3,77 and p = ,001**			Z = -,358 and p = ,72		
	Family Involvement (pretest)	85,94 ± 14,71	37,50	100	74,57 ± 18,25	25,00	100
	Family Involvement (posttest)	89,87 ± 16,98	25,00	100	72,77 ± 16,76	43,75	100
		Z = -2,347 and p = ,019***			Z = -1,462 and p = ,144		
	Communication (pretest)	77,77 ± 2,97	35,00	100	66,38 ± 19,34	25,00	100
	Communication (posttest)	85,89 ± 17,96	25,00	100	64,05 ± 2,64	5,00	100
		Z = -3,527 and p = ,001**			Z = -1,555 and p = ,12		
	Technical skills (pretest)	83,52 ± 17,76	37,50	100	71,59 ± 19,01	,00	100
	Technical Skills (posttest)	85,84 ± 21,83	,00	100	67,94 ± 19,54	,00	100
		Z = -1,404 and p = ,16			Z = -2,574 and p = ,01***		
	Emotional Needs (pretest)	71,23 ± 24,62	25,00	100	56,59 ± 25,73	,00	100
	Emotional Needs (posttest)	78,03 ± 25,53	,00	100	54,40 ± 27,04	,00	100
		Z = -1,62 and p = ,105			Z = -1,3 and p = ,194		
	General Satisfaction (pretest)	89,58 ± 13,82	41,67	100	73,86 ± 17,29	41,67	100
	General Satisfaction (posttest)	92,80 ± 13,76	25,00	100	7,83 ± 18,28	41,67	100
		Z = -1,228 and p = ,22			Z = -1,78 and p = ,075		
	PedsQL Total (pretest)	477,02 ± 98,13	221,67	600	411,58 ± 98,53	22,00	600
	PedsQL Total (posttest)	511,62 ± 95,25	15,00	600	399,67 ±101,87	228,33	600
		Z = -2,798 and p = ,005***			Z = -1,855 and p = ,064		
SIPS	SIPS Total (pretest)	27,34 ± 13,08	1	48	24,34 ± 1,27	7	48
	SIPS Total (posttest)	22,48 ± 13,64	,00	48	25,09 ± 1,23	5,00	48
		Z = -2,867 and p = ,004***			Z = -,444 and p = ,657		

* Wilcoxon test, ** p < .001, *** p < .05

It was seen in the examination of the PedsQL Healthcare Satisfaction Scale that there was a significant difference between the participants in the 3D-TND group (p=0.005). In the pretest-posttest comparison of the PedsQL of the participants in the SND group, there wasn't significant difference (p=0.064). In the results of the pretest-posttest comparisons of the subscales of the PedsQL, it was seen that the 3D-TND group had significant differences in the receiving information (p=0.001), family involvement (p=0.019), and communication (p=0.001) subscales while only the technical skills subscale displayed a significant difference (p=0.01) in the SND group. The results of the comparisons of the pretest-posttest values of the scales in the 3D-TND and SND groups in Table 4. Accordingly, there wasn't significant difference between the *SIPS pretest* results (p=0.197) and the *SIPS posttest* (p=0.159) in the comparison of the 3D-TND and SND groups.

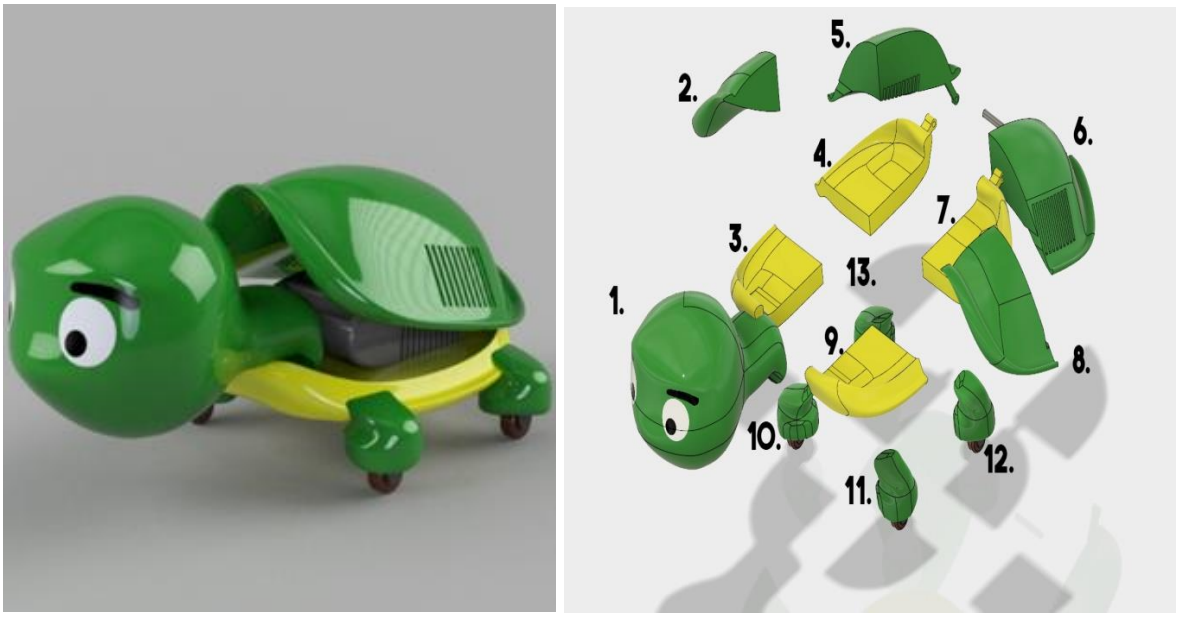

Figure 1. Therapeutic Nebulizer - model Fusion 360, parts.

Table 4. Mann-Whitney U Test Results of Intergroup Comparisons of Pre- and Posttest Scores

		Pretest			Posttest		
		Mean ± SD	Min	Max	Mean ± SD	Min	Max
PedsQ Healthcare Satisfaction Scale	**Receiving information 3D-TND**	72,22 ± 23,40	15,00	100	82,74 ± 17,51	25,00	100
	Receiving information SND	69,86 ± 18,69	2,00	100	69,66 ± 17,76	3,00	100
		Z = -,496 and p = ,062			Z = -3,432 and p = ,001**		
	Family Involvement 3D-TND	85,94 ± 14,71	37,50	100	89,87 ± 16,98	25,00	100
	Family Involvement SND	74,57 ± 18,25	25,00	100	72,77 ± 16,76	43,75	100
		Z = -3,032 and p = ,002***			Z = -4,736 and p = ,001**		
	Communication 3D-TND	77,77 ± 2,97	35,00	100	85,89 ± 17,96	25,00	100
	Communication SND	66,38 ± 19,34	25,00	100	64,05 ± 2,64	5,00	100
		Z = -2,523 and p = ,012***			Z = -1,555 and p = ,12		
	Technical Skills 3D-TND	83,52 ± 17,76	37,50	100	85,84 ± 21,83	,00	100
	Technical Skills SND	71,59 ± 19,01	<,001	100	67,94 ± 19,54	<,001	100
		Z = -3,234 and p = ,001**			Z = 4,486 and p = ,001**		
	Emotional Needs 3D-TND	71,23 ± 24,62	25,00	100	78,03 ± 25,53	,00	100
	Emotional Needs SND	56,59 ± 25,73	<,001	100	54,40 ± 27,04	<,001	100
		Z = -2,659 and p = ,008***			Z = -3,884 and p = ,001**		
	General Satisfaction 3D-TND	89,58 ± 13,82	41,67	100	92,80 ± 13,76	25,00	100
	General Satisfaction SND	73,86 ± 17,29	41,67	100	70,83 ± 18,28	41,67	100
		Z = -4,319 and p = ,001**			Z = -5,625 and p = ,001**		
	PedsQL Total 3D-TND	477,02 ± 98,13	221,67	600	511,62 ± 95,25	15,00	600
	PedsQL Total SND	411,58 ± 98,53	22,00	600	399,67 ±101,87	228,33	600
		Z = -3,014 and p = ,003***			Z = -4,855 and p = ,001**		
SIPS	**SIPS Total 3D-TND**	27,34 ± 13,08	1	48	22,48 ± 13,64	,00	48
	SIPS Total SND	24,34 ± 1,27	7	48	25,09 ± 1,23	5,00	48
		Z = -1,291 and p = ,197			Z = -1,408 and p = ,159		

* Mann-Whitney U test, ** p < .001, *** p < .05

In the examination of the findings regarding the PedsQL Healthcare Satisfaction Scale, it was seen that the *"PedsQL pretest* scores (p=0.003) and *PedsQL posttest* scores (p=0.001) didn't display a significance difference when the 3D-TND and SND groups were compared. A comparison was made of the 3D-TND and SND groups in terms of their pretest and posttest scores for the subscales of the PedsQL Healthcare Satisfaction scale. In the *PedsQL pretest,* it was found that when the 3D-TND and SND groups were compared, outside of the subscale Receiving Information, all dimensions displayed significant differences. In the *PedsQL posttest,* it was found that when the 3D-TND and SND groups were compared, all of the subscales showed significant differences.

DISCUSSION

Discussion of findings related to psychosocial symptoms

Inhalation therapy is a technique that is commonly used in children in the event of acute asthma attacks, bronchiolitis, bronchitis, pneumonia, cystic fibrosis and other similar respiratory system conditions (4,6,17). The devices employed in this treatment are commonly of the standard type, an apparatus that generates a loud sound and looks formidable to children. Being in the hospital for some medical condition and being exposed to unfamiliar surroundings and devices lead to the emergence of psychosocial symptoms in children (2,6). The results of this study show that treatment delivered with the 3D-TND produces fewer psychosocial symptoms than therapy with an SND. While children who receive therapy with an SND exhibit symptoms of crying, fearfulness or the desire to escape the treatment, it has been concluded that children's psychosocial symptoms are reduced when 3D-TND therapy is implemented. A scan of the literature didn't uncover any study that was conducted using a nebulizer based on 3D printing technology. The results of the study were therefore supported with the reports of only similar findings. Nijhof et al. (2018) reports a study that was carried out to provide educational support to hospitalized children willing to participate in the research for the purpose of reducing their psychosocial symptoms. It was concluded that participation in educational activities instigated a rise in the children's favorable attitude toward the hospital, mitigated their fearfulness and allowed them to spend a more cheerful time at the hospital.

Yanık & Ayyıldız (2019) used a toy-type nebulizer device in children receiving nebulizer treatment and stated that anxiety and fear decreased significantly in children receiving treatment with a toy-type nebulizer. In the same study, it was concluded that crying and fear continued significantly in children receiving standard-type nebulizer treatment. In the study conducted by

Kırkan & Kahraman (2023), in which the fear and anxiety levels of children were evaluated using a toy nebulizer and a toy mask, it was concluded that there was a significant decrease in children's fear and anxiety.

Silva et al. (2020) examined the effect of therapeutic play and toy use on children's fear and anxiety in children receiving inhaler treatment. It was observed that fear and anxiety decreased significantly in children receiving inhaler treatment through therapeutic toys. In their study with a toy nebulizer device, Kırkan & Kahraman (2023) concluded that children who previously cried while receiving treatment did not cry while receiving treatment with the therapeutic device.

In a review of the literature, it was seen that Nijhof et al. (2018), Sağlık & Çağlar (2019), Silva et al. (2017) and Üstün et al. (2014) made use of various therapeutic approaches to reduce the adverse effects of illness and hospitalization on children. Sağlık & Çağlar (2019) used a picture-drawing method as a projective technique to reduce what appeared to be hospital-related symptoms in children and reported that feelings of fear, anxiety, depression and similar negative emotions were less frequent among the children (22-24). Stated that it was necessary for the sake of protecting pediatric health to make an early identification of any psychosocial symptoms hospitalized children may have. Toward this aim, the researchers developed an inventory to identify psychosocial symptoms that proved to determine psychosocial symptoms earlier than other measuring tools. It may be said that early identification of symptoms will allow for easier and earlier symptom management.

Discussion related to SIPS results

In the pretest-posttest comparisons of the 3D-TND and SND groups in this study, a significant difference was seen between the SIPS mean scores in the 3D-TND group but not in the SND group. In the comparison of the pretest and posttest mean scores in groups, however, no significant difference was observed between the SIPS mean scores. The common practice in the hospital of delivering medication via a nebulizer is seen to cause prevalent anxiety because of the appearance and sounds of the device (2,11,24). Kırkan & Kahraman (2023) found a significant difference in children's fear and anxiety after inhaler treatment with therapeutic play. Similar results are also seen in the studies conducted by Coşkuntürk & Gözen (2018) and Durak & Uysal (2021) (27,29).

Potasz et al. (2013) have devised games to reduce stress among hospitalized children with respiratory diseases. The authors found that toys and games can make the commonly

implemented nebulizer therapy much more tolerable for children, thereby increasing their compliance and reducing their stress. The study revealed that children adapted much more easily to hospital routines, clinical circumstances and devices with a toy type of nebulizer and that compared to children receiving therapy with a standard type of device, these children exhibited a lesser frequency of psychosocial symptoms.

Yanık and Ayyıldız (2018) examined the effect of using toy-type nebulizers on anxiety in children aged 3-6 and concluded that the use of toy-type nebulizers reduced anxiety in children. Jones et al. (2017) conducted a study in an effort to meet the needs of hospitalized children and their parents, working to determine their levels of anxiety and stress. According to the study, it was found that using child-friendly types of devices as well as tantalizing surroundings that address children during their stay at the hospital reduces stress and anxiety in both children and their parents.

Similar studies such as of Chen et al. (2014), Silva et al. (2017) and Suryawanshi et al. (2016) have studied the effects of therapeutic toys and games on anxiety, stress and fear levels of hospitalized children. The increase in adaptation to therapy and the reduced fear and anxiety found in these studies are similar. Ibfelt et al. (2015) and Paladino et al. (2014) studied the use of therapeutic toys by pediatric nurses. It was found that therapeutic toys diminished the use of medications among children and reduced anxiety, fear and other psychosocial symptoms. Studies in the literature reveal that hospitalized children suffer fear, anxiety and other psychosocial symptoms such as crying because of their experiences with their illness, being in a hospital, having to remain in unfamiliar surroundings, and undergoing medical treatment with various devices (20,25). The results of our study are consistent with what is reported in the literature.

Discussion of PedsQL Healthcare Satisfaction Scale results

When a child needs to be hospitalized, significant changes occur in the whole family's lifestyle. These changes cause all family members to experience fear, anxiety, stress, or crisis. Factors that cause these conditions include having anxiety about the child’s recovery, being unfamiliar with the hospital environment, finding themselves useless in the care of the child, and feeling guilty. Parental satisfaction is defined in childcare as fulfilling the perceived positive expectations of the family (23,29,30).

Silva et al. (2017) and Teksoz et al. (2017) conducted a study in order to examine the fear, anxiety and healthcare satisfaction of parents of hospitalized children. They noted a high level of healthcare satisfaction among parents with children in the hospital who had been encouraged to adapt to treatment and provided education and increased communication by nurses. It was reported that when children were encouraged to participate in their own treatment and care, this resulted in higher parental healthcare satisfaction. In the study by Kapkin et al. (2020) and Teksoz et al. (2017) parents of hospitalized children were invited to participate in their child's care actively. The parents participated in feeding, dressing, diagnosing, treating, breathing exercises and steam applications, and it was observed that their healthcare satisfaction scores rose significantly, both in the overall scale and in all the subscales. This finding is consistent with the results of our study. Drayton et al. (2019) concluded that parents of children whose needs were met in the hospital were likely to have higher scores in terms of satisfaction with healthcare.

The literature acknowledges the importance of information for parents and their presence during interventions as this can reduce anxiety and increase parents' satisfaction with care (28-30). Specifically, although it has become common practice for parents to stay with their sick child in the hospital, most hospitals lack the routines and staff guidelines for involving parents in care processes and decisions (23,31). Studies that have worked with parents becoming involved in their child’s care and treatment have indicated that parental stress, anxiety and other psychosocial symptoms are diminished and parental healthcare satisfaction increases.

Klinnert wt al. (2008) conducted a study with parents of children hospitalized due to asthma treatment and found that parents' satisfaction and emotional states varied according to their children's reactions to the treatment process. Volerman et al. (2023) examined the satisfaction levels of parents of children hospitalized for asthma treatment. They found that the communication and satisfaction levels of parents of children without psychosocial symptoms during inhaler treatment were high. These findings are similar to the findings of our study.

Fisher & Broome (2011) report that parents who are included in the process of their children’s treatment and care while in the hospital and are kept in the communication loop have increased satisfaction with the care provided. Cimke (2017) included families in the process of care given to children in their study and examined the satisfaction with care in both the child and the parents. They concluded that being at the child’s side, being involved during postural drainage, breathing exercises and nebulizer therapy resulted in the parents’ exhibiting markedly high

scores in terms of satisfaction with healthcare. In their examination of interventions carried out with the aid of creative games, Teksoz et al. (2017) found that this effort impacted satisfaction with care. The results of these studies in the literature are consistent with the outcome of our study.

CONCLUSIONS

With this study, we concluded that the 3D therapeutic nebulizer developed to reduce the psychosocial symptoms of children being administered nebulizer therapy was more effective in lessening these symptoms than the standard type of nebulizer machine. Using 3D printing technology in the effort to reduce the treatment-related psychosocial symptoms of sick and hospitalized children is an innovative approach that can be used.

Limitation

The inability to conduct the study at both hospitals also constituted one of its limitations. The study had to be conducted only in one institution because only one 3D-TND, which the researcher produced, was available. At the same time, the two hospitals were at an inconvenient distance from each other, and the device could obviously not be carried to the second institution while the treatment was ongoing in the first one. This situation constituted the limitation of the research.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Kolesistektomi Sonrası Biliyer Kaçak Gelişen Hastalarda Biliyer Stent ve Nazobiliyer Drenin Karşılaştırılması

Comparison of Biliary Stent and Nasobiliary Drain in Patients with Biliary Leak After Cholecystectomy

Mehmet Raşit AYTE [1*], İlhami YÜKSEL [2]
[1] Ankara Atatürk Sanatoryum Eğitim Araştırma Hastanesi, Gastroenteroloji Kliniği, Ankara, Türkiye
[2] Ankara Yıldırım Beyazıt Üniversitesi, Gastroenteroloji Kliniği, Ankara, Türkiye

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Özet

Amaç: Kolesistektomi sonrası gelişen biliyer kaçak tedavisinde Endoskopik Retrograd Kolanjiyopankreatografi (ERCP) ile yerleştirilen biliyer stent veya nazobiliyer dren (NBD) tercih edilen prosedürlerdir. Çalışmamızda, biliyer kaçak tespit edilen hastalarda NBD veya biliyer stentin etkinliğini karşılaştırmayı amaçladık.

Yöntem: Postkoleksistektomi safra kaçağı olan 37 hasta çalışmaya dahil edildi. 20 hastaya biliyer stent, 17 hastaya NBD uygulandı. Hastalar; ek işlem gereksinimi, ERCP komplikasyonları, hastanede yatış süresi, toplam takip süresi açısından karşılaştırıldı.

Bulgular: Biliyer stent uygulanan 20 hastanın 11'inde (%55) sistik güdükten, 5'inde (%25) Luschka'dan, 4'ünde (%20) lateral duvardan kaçak vardı. Hastanede yatış süresi 10,5 ± 7 gün iken, toplam takip süreleri 89,9 ± 42,8 gündü. NBD uygulanan 17 hastanın 10'unda (%58,8) sistik güdükten, 4'ünde (%23,5) luschka'dan, 2'sinde (%11,7) lateral duvardan, 1'inde (%5,8) sağ segmental duktustan kaçak vardı. Hastanede yatış süresi 11,9 ± 3,2 gün iken, toplam takip süreleri 31,5 ± 11,7 gündü. Ayrıca kaçak lokalizasyonuna göre; 1. grupta (Strazberg tip A) hospitalizasyon süresi 9 ± 2,3 gün, toplam takip süresi 54,0 ± 6.7 iken, 2. grupta (Strazberg tip A dışı) hastanede yatış süresi 16,9 ± 2,7 gün, toplam takip süreleri 84 ± 40,2 gündü.

Sonuç: Biliyer stent uygulanan hastalarda, hastanede yatış süresinin daha kısa olduğu ve komplikasyonların daha az geliştiği, tespit edildi. NBD'li hastalarda toplam takip süreleri daha kısaydı. Ayrıca çalışmamız uygulanacak modalitenin belirlenmesinde kaçak yerinin de göz önüne alınması gerektiğini düşündürmektedir.

Anahtar Kelimeler: Biliyer kaçak, Biliyer stent, Kolesistektomi, Nazobiliyer dren

Abstract

Objective: Biliary stent or nasobiliary drain (NBD) placed by Endoscopic Retrograde Cholangiopancreatography (ERCP) are the preferred procedures in the treatment of biliary leak that develops after cholecystectomy. In our study, we aimed to compare the effectiveness of NBD or biliary stent in patients with biliary leakage.

Materials and method: 37 patients with postcholecystectomy bile leaks were included in the study. Biliary stent was applied to 20 patients and NBD was applied to 17 patients. Patients; They were compared in terms of need for additional procedures, ERCP complications, hospital stay, and total follow-up time.

Results: Of the 20 patients to whom biliary stent was applied, 11 (55%) had leakage from the cystic duct, 5 (25%) had leakage from the Luschka, and 4 (20%) had leakage from the lateral wall. While the hospitalization time was 10.5 ± 7 days, the total follow-up time was 89.9 ± 42.8 days. Of the 17 patients who underwent NBD, 10 (58.8%) were from the cystic duct, 4 (23.5%) were from the Luschka, 2 (11.7%) were from the lateral wall, and 1 (5.8%) was from the right segmental duct. The hospitalization period was 11.9 ± 3.2 days and the total follow-up period was 31.5 ± 11.7 days. Additionally, depending on the leak location; In the 1st group (Strasberg type A), the hospitalization time was 9 ± 2.3 days and the total follow-up time was 54.0 ± 6.7 days, while in the 2nd group (non-Strasberg type A), the hospitalization time was 16.9 ± 2.7 days and the total follow-up time was 84±40.2 days.

Conclusion: It was observed that the hospital stay was shorter and complications were less common in patients who received biliary stents total follow-up times were shorter in patients with NBD. Additionally, our study shows that the location of the leak is also important when determining the procedure to be applied.

Keywords: Biliary leak, Biliary stent, Cholecystectomy, Nasobilier drain

***Sorumlu Yazar / Corresponding Author:** Mehmet Raşit AYTE, Sağlık Bilimleri Üniversitesi Ankara Atatürk Sanatoryum Eğitim Araştırma Hastanesi, Gastroenteroloji Kliniği, Ankara, Türkiye **E-mail**: mehmetrasit.md@gmail.com

GİRİŞ

Safra yolları yaralanmaları laparoskopik kolesistektomi sonrası %0,4-0,6, açık cerrahi sonrası %0,1-0,2 oranında görülür (1, 2). Safra yolu yaralanmalarının %49'u intraoperatif olarak fark edilirken, %51'i postoperatif dönemde fark edilmektedir (3). Postkolesistektomi biliyer kaçağın yönetiminde; peroperatif ve operasyon sonrası takipte, girişimsel radyololojik prosedürlerde ve endoskopik girişim ile tedavide deneyimin artmış olması nedeniyle ilerleme kaydedilmiştir. Endoskopik retrograt kolanjio-pankreatografi (ERCP), tanı ve biliyer kaçağın etkin tedavisinde tercih edilen minimal invaziv yöntemdir. ERCP ile tedavi safra yolunun kateterizasyonu, endoskopik sfinkterotomi (EST), geçici olarak biliyer stent veya nazobiliyer dren (NBD) yerleştirilmesini içerir. NBD, ERCP sonrası takip aşamasında biliyer drenajın değerlendirilmesi için safra yolarına kolanjiografik girişim olanağı sağlar. Hasta intoleransı ve elektrolit dengesizlikleri NBD'ın yan etkileridir. Biliyer stent uyumsuz hastalarda daha kullanışlı olmakla birlikte, biliyer stentte stentin çıkarılması için ikinci bir ERCP'ye ihtiyaç vardır. Her iki modalitenin kullanılabilirliğine rağmen, rölatif güvenilirliği, maliyet ve etkinliği tam olarak bilinmemektedir. Çalışmamızın amacı biliyer kaçak tespit edilen ve NBD veya biliyer stent uygulanan hastaları ERCP komplikasyonları, ERCP sonrası hastanede kalış süresi, taburculuk sonrası takip süreleri açısından karşılaştırmaktı.

GEREÇ VE YÖNTEMLER

Bu çalışma, tek merkezli bir deneyime dayanmaktadır. Ocak 2008 ve Mayıs 2014 tarihleri arasında ERCP yapılan hastalar hastanemizin veri tabanı aracılığı ile elektronik ortamda retrospektif taranarak bulundu. Yıllara göre ERCP sayıları ve kaçak tespit edilen hastalar belirlendi. Sadece ERCP ile kesin kanıtlanmış postkolesistektomi safra kaçağı olan hastalar çalışmaya dahil edildi. Kolesistektomi dışındaki farklı bir nedene bağlı gelişen safra kaçakları çalışma dışı bırakıldı.

Tüm hastaların demografik özellikleri kayıt edildi. Kaçak tespit edilen hastaların kaçağa neden olan operasyon şekli, semptomları, prezentasyonları, ERCP sonrası takiplerde komplikasyon gelişip gelişmediği, Strazberg-Bizmut klasifikasyonu kullanılarak kaçak sınıflaması, kaçak derecesi, kaçak yeri, ERCP den sonra hastanede yatış süresi ve taburculuk sonrası takip süresi hasta epikrizleri taranarak bulundu. Kontrast sonrası floroskopi ile intrahepatik safra yolları (İHSY) nın görüldüğü hastalar düşük dereceli, görülmediği hastalar yüksek dereceli kaçak olarak kabul edildi.

Verilerin istatistiksel analizi Statistical Package for Social Science (SPSS) versiyon 18 bilgisayar programı kullanılarak yapıldı. Nazobiliyer dren ve biliyer stent uygulanan hastalarda kategorik değişkenler açısıdan gruplar arasında fark olup olmadığını tespit etmek için Ki-kare veya Fisher testleri kullanıldı. Normal dağılım gösteren sayısal veriler için T-testi, normal dağılım göstermediği belirlenen veriler Mann-Whitney U testi ile karşılaştırıldı. P değeri 0,05'ten küçük olduğunda istatistiksel olarak anlamlı kabul edildi.

BULGULAR

Hasta özellikleri:

Safra kaçağı olan hastalarda stent ve nazobiliyer drenajın etkinliğinin karşılaştırılması.

Tablo 1. Safra kaçağı olan 37 hastanın demografik özellikleri

Demografik Bulgular	n:37
Ortalama yaş	52,2 ± 11,3 (yıl)
Kadın / Erkek	28 / 9
Prezentasyon	
Drenden safra kaçağı	34 (%91,8)
Karın ağrısı	34 (%91,8)
Ateş	7 (%18,9)
Sarılık	6 (%16,2)
Anormal karaciğer fonksiyon testleri	20 (%54,0)
Kolesistektomi	
Açık	10 (%27,1)
Laparoskopik	27 (%72,9)

Hastanemizde 1 Ocak 2008 ile 31 Mayıs 2014 yılları arasında 2.212 ERCP yapılan hasta tespit edildi ve retrospektif tarandı. 60 hastaya kaçak nedeniyle ERCP yapıldı. Bunların 52'sinin (%86,6) etyolojisinde postkolesistektomi biliyer kaçak vardı. 37'sinin tüm verilerine ulaşıldı.

Ortalama yaşları 52,2 ± 11,3 yıl olan 37 hastanın 27'sine (%72,9) laparoskopik kolesistektomi (LK), 10'una (%27,1) açık kolesistektomi (AK) yapılmıştı. Hastaların 34'ünde (%91,8) karın ağrısı, 18'inde (%48,6) bulantı-kusma, 7'sinde (%18,9) ateş, 6'sında (%16,2) sarılık, 1'inde (%2,7) kaşıntı şikayetleri vardı. Hastaların 3'ü (%13,5) asemptomatikti ve bu hastalarda biliyer

kaçak tanısı drenden safra geleni olması üzerine şüphelenilip ERCP yapılarak kondu. Her hastaya ultrasonografi (USG) yapıldı. 17 (%45,9) hastada kaçak lehine bulgu (kese lojunda mayi) saptandı. 34 (%91,8) hastada dren takibinde safralı drenaj oldu. 20 (%54.05) hastada enzim yüksekliği, 7 (%18,9) hastada hiperbilirubinemi tespit edildi. 4 (%10,8) hasta pankreatit, 2 (%5,4) hastanın kolanjit bulguları (ateş, karın ağrısı, bilirubin yüksekliği) mevcuttu.

Endoskopik prosedürler:

37 hastanın 20'sine stent takıldı. 17'sine NBD uygulandı. Biliyer Stent (BS) uygulanan hastalarda yaş ortalaması 54,9 ± 16,3 yıl, NBD uygulanan hastalarda 49,3 ± 13,6 tespit edildi. Biliyer stent 13 (%65) kadın, 7 (%35) erkek hastaya uygulanırken, NBD 15 (%88,2) kadın, 2 (%11,8) erkek hastaya uygulandı.

Biliyer stentli hastaların 15'inde (%75) LK, 5'inde (%25) AK yapılmıştı. NBD uygulanan hastaların 12 (%70,5)'sinde LK, 5'inde (%29,5) AK yapılmıştı.

Endoskopik tedavi sonuçları ve uzun dönem takipler:

Tablo 2. Safra sızıntısının özellikleri, yeri ve şiddeti. Biliyer stent ve nazobiliyer drenajın etkinliğinin inatçı safra kaçağı, tekrarlanan ERCP işlemi, hastanede kalış süresi ve cerrahiye göre karşılaştırılması

	Biliyer Stent n:20 (%54)	**Nazobiliyer Dren n:17 (%46)**	**Toplam n:37**
Yaş ortalaması	54,9 ± 16,3 (yıl)	49,3 ± 13,6 (yıl)	52,2 ± 11,3 (yıl)
Biliyer kaçak lokasyonu			
Sistik güdük	11 (%55)	10 (%58,8)	21 (%56,7)
Lutcka	5 (%25)	4 (%23,5)	9 (%24,3)
Lateral duvar	4 (%20)	2 (%11,7)	6 (%16,2)
Sağ segmental biliyer duktus	0	1 (%5,8)	1 (%2,7)
Strazberg sınıflaması			
A	16 (%80)	14 (%82,3)	30 (%81)
D	4 (%20)	2 (%17,6)	6 (%16,2)
E5		1 (%5,8)	1 (%2,7)
Biliyer kaçağın şiddeti			
Düşük derece	13 (%65)	12 (%70,5)	25 (%67,5)
Yüksek derece	7 (%35)	5 (%29,5)	12 (%32,5)

Devam eden biliyer kaçak	2 (%10)	3 (%17,6)	5 (%13,5)
Pankreatit	2 (%10)	5 (%29)	7 (%18,9)
ERCP tekrarı gereksinimi	1 (%5) NBD ile kür sağlandı	2 (%11,7) biliyer stent ile kür sağlandı	3 (%8,1)
Cerrahi gereksinimi	1 (%5) pnömosepsis nedeniye ölüm	1 (%5,8) Operasyon sonrası kür sağlandı	2 (%5,4)
Hastanede yatış süresi	10,5 ± 7 gün	11,9 ± 3,2 gün	
Toplam takip süresi [a]	89,9 ± 42,8 gün	31,5 ± 11,7 gün	

a= (p<0,001)

Kaçağın derecesi belirlenirken İHSY'nın görüldüğü kaçaklar düşük dereceli, İHSY'nın görülmediği kaçaklar ise yüksek dereceli olarak değerlendirildi. İHSY biliyer stentli hastaların 13'ünde (%65) NBD'li hastaların 12'sinde (%70,5) görülebiliyorken, biliyer stentli hastaların 7'sinde (%35) ve NBD'lilerin 5'inde (%29,5) görülemiyordu.

NBD ve biliyer stent uygulanan hastalar post ERCP komplikasyon açısından karşılaştırıldı. Biliyer stentli hastaların 2'sinde (%10) pankreatit gelişirken, NBD'li hastaların 5'inde (%29) gelişti (p=0,212). İstatistiksel olarak anlamlı olmasa da NBD'li hastalarda işlem sonrası komplikasyonun daha çok geliştiği görüldü.

İkinci bir işlem gerekenler (operasyon veya ikinci bir ERCP gerekenler) veya gerekmeyenler sonuç başlığı altında değerlendirildi. Biliyer stentli ve NBD'li gruplar sonuç açısından karşılaştırıldı. Biliyer stentli hastaların 2'sinde (%10) ikinci bir işlem gerekti. Bir hastaya devam eden kaçak nedeniyle stent ile birlikte 7F NBD tüpü uygulandı. Takibin 12'nci gününde hastada yapılan kolanjiogramda kaçağın kapandığı gözlendi ve NBD tüpü çekildi. Takiplerinde ek bir komplikasyon gelişmeyen hastada ilk ERCP'den 84 gün sonra stent çıkarıldı. Diğer hastada başarılı bir operasyon sonrası kaçak geriledi. Ancak takibinin 14. gününde pnömosepsis nedeniyle ex oldu. NBD'li hastaların 3'ünde (%17,6) ikinci bir işlem gerekti. Bu hastaların ikisinde biliyer stent (birine 7.5F, diğerine 7F biliyer stent) ile ve birinde başarılı bir operasyon ile kaçak geriledi. NBD'li hastalarda daha fazla ikinci bir işleme gerek oldu.

Her iki grup hastanede yatış süreleri açısından karşılaştırıldı. Biliyer stentli hastalar 10,5 ± 7 gün yatarken NBD'li hastalar 11,9 ± 3,2 gün yattı (p=0.52).

Her iki grup ERCP sonrası takip açısından değerlendirildiğinde; biliyer stentli grup 89,9 ± 42,8 gün takip edilirken, NBD'li grup 31,5 ± 11,7 gün takip edildi (p<0.001).

Tablo 3. Hastaların yatış ve takip sürelerine göre değerlendirilmesi

	Strasberg-Bizmut sınıf A (Sistik güdük veya Luschka)	Strasberg-Bizmut sınıf D veya E5 (Diğer)
Hastanede yatış süresi	9 ± 2,3	16,9 ± 2,7
Toplam takip süresi [b]	54,0 ± 6,7	84 ± 40,2

b=(p=0,005)

Hastaların strasberg kalsifikasyonuna göre kaçak lokalizasyonları belirlendi. 21 (%56,7) hastada sistik güdükten (tip A), 9 (%24,3) hastada Luschka'dan (tip A), 6 (%16,2) hastada lateral duvardan (tip D) ve 1 (%2,7) hastada sağ hepatik ductustan (tip E5) kaçak tespit edildi. Sistik güdük veya luchka'dan (tip A) kaçak olan 30 hastanın 16'sına (%53,3) biliyer stent, 14'üne (%46,6) NBD uygulandı. Tip D grubun 4'üne (%66,6) biliyer stent, 2'sine (%33,3) NBD ve tip E5 grubunda olan bir hastaya da NBD uygulandı. Hastalar biliyer kaçağın daha sık görüldüğü tip A grup ve tip A dışı grup (tip D ve tip E5) olarak 2 gruba ayrıldı. Hastanede yatış süresi bakımından; 1.Grup (tip A) 9 ± 2,3 gün iken 2. Grup (tip A dışı) 16,9 ± 2,7 gün idi (p=0,005).

TARTIŞMA

Günümüz pratiğinde biliyer kaçak özellikle laparoskopik kolesistektomi başta olmak üzere hepatobiliyer operasyonların komplikasyonu olarak görülür. Kaçak nedeniyle sızan safra; peritonit, abse gibi mortalitesi yüksek sonuçlara sebep olabilir (4,5). Cerrahi tedavi, komplikasyonların gelişme ihtimalinin yüksek olması nedeniyle zor ve risklidir (6).

Postoperatif dönemde safra kaçağından şüphelenildiğinde, tanıyı doğrulamak, kaçağın tam yerini saptamada ve tıkayıcı safra taşlarının varlığını ekarte etmede biliyer sistemin ERCP ile görselleştirilmesi çok önemli bir yere sahiptir. Konvansiyonel kolesistektomi sonrası gelişen biliyer kaçak tedavisinde uygulanan cerrahi müdahalede mobidite %11, mortalite %37'dir (7,8). NBD, BS, EST ve /veya bunların kombinasyonlarından oluşan birçok çeşitli endoskopik prosedürler mevcuttur. Endoskopik girişimde amaç oddi sfinkter basıncının düşürülmesi ile koledok ve duodenum arasındaki basınç gradiyentinin düşürülmesidir. Bu işlemle kaçak engellenip duodenuma drenaj sağlanır ve fistül kapatılır (9-10). Biliyer ağacın dikkatli muayenesi zorunludur, çünkü altta yatan biliyer obstrüksiyon, duktal defekti devam ettirebilir veya kötüleştirebilir. Bununla birlikte, biliyer sızıntının ve endoskopik tedavisinin uzun vadeli komplikasyonları bilinmemektedir. NBD biliyer kaçakta kullanılan bir endoskopik tedavi modalitesidir. NBD'nin avantajları, ek bir endoskopik girişim olmadan çıkarılabilmesi ve

kolanjiyografi yapılabilmesidir. Dezavantajları; hastada konforsuzluk, sıvı ve elektrolit kaybı, hastanede yatış süresinin fazla olmasıdır (11). Bazı çalışmalar BS'nin daha kısa zaman zarfında fistülün kapanması açısından üstün olduğunu göstermektedir (12). Bir vaka serisinde endoskopik sfinkterotomi, biliyer kaçakların tedavisi için değerlendirilmiş ancak stent veya drenaj yerleşiminden daha az etkili görünmüştür (13). Biliyer sistemi patent hastalarda sfinkterotomiden kaçınılması gerekebilir, böylece kanama, perforasyon, pankreatit veya sfinkterotomi bölgesinin darlığı gibi kısa ve uzun vadeli riskler ortadan kaldırılabilir. Başka bir çalışmada stent çapının biliyer sızıntıların tedavisi için önemli olmadığı ve 7F stentlerin bu amaç için yeterli olduğu sonucuna varmıştır(14). BS ve NBD'nin birbirinden bağımsız olarak etkili olduğu bilinmesine rağmen bunların karşılaştırmalı güvenilirlikleri ve maliyet etkinlikleri üzerine yeterli çalışma bulunmamaktadır

Postkolesistektomi biliyer kaçak gelişen hastalarda ERCP ile biliyer stent ve NBD uygulanan hastaları geriye dönük olarak karşılaştırdık.

Çalışmamız, biliyer sızıntının endoskopik tedavisinin etkili olduğunu göstermektedir 37 hastanın dahil edildiği çalışmada %100 başarıyla kanülizasyon yapıldı. 2 yıldan uzun bir süre takip edildiklerinde, tekrarlayan safra sızıntısı olmadığı görüldü. Kür açısından BS'in NBD'e kısmen üstün olduğunu ve NBD'e kıyasla daha az ikinci bir işlem gerektiğini tespit ettik. NBD'li hastalarda komplikasyon daha çok gelişti.

NBD takılan hastalar daha uzun süre hastane yatışı olurken, takipleri daha kısa sürdü. Taburculuk sonrası takip amacıyla ek bir girişim gerekmedi. Fakat hastalar için konforsuz bir işlemdi. BS'li hastalar daha az süre ile hastanede yatmış olsalar da daha uzun süre takip edildi ve takipte stent kontrolü veya stentin çekilmesi için ek bir girişime ihtiyaç oldu. NBD'ye nazaran daha konforlu bir işlemdi. Bu sonuçlara göre; maliyet etkinlik açısından NBD daha uygun olsa da, hastanede yatış süresi uzaması ve konforsuz olması nedeniyle, safra kaçağı olgularında biliyer stentin de güvenli bir şekilde kullanılabileceği akılda bulundurulmalıdır.

Ayrıca sistik kanal veya luchka'dan kaçak tespit edilen (strazberg klasifikayonuna göre tip A: 1. grup) hastalar, bilier sistemin diğer lokalizasyonlarında kaçak tespit edilenlere (2. Grup) göre daha kısa süreli hospitalizasyona ihtiyaç duydu. Bu sonuç; uygulanacak modalitenin belirlenmesinde kaçak yerinin de gözönüne alınması gerektiğini, ikinci gruptaki hastalarda NBD yerine hastanede yatış süresi daha az olan biliyer stentin tercih edilmesinin daha uygun olabileceğini düşündürmektedir.

Çalışmamız retrospektif bir çalışmadır. Veri kaybı nedeniyle çalışmaya dahil edilemeyen hasta sayısı fazlaydı ve bu nedenle çalışmaya dahil edilebilen vaka sayısı azdı. Stent takılan hastaların stentin çıkarılması için yapılacak ikinci ERCP'nin günü standart değildir. Erken çekilen biliyer stentler iyileşmemiş bir fistül açığa çıkarabilirken, çok geç çekilenler tıkanmaya neden olabilir. Nazobiliyer drenli hastaların drenlerinin çekileceği zamanın ve BS'li hastaların stentlerinin çekileceği ikinci ERCP'nin süresinin standardize edildiği ve her iki modaliteyi daha iyi kıyaslayabilmek için vaka sayısının daha fazla olduğu geniş serili prospektif çalışmalara ihtiyaç vardır.

SONUÇ

Bu çalışma ile biliyer kaçak olgularında; hem NBD hem de biliyer stent uygulamasının tedavide etkin olduğu gösterilmiştir. Biliyer stent uygulanan hastalarda, hastanede yatış süresinin daha kısa olduğu ve komplikasyonların daha az geliştiği, tespit edilmiştir. Biliyer stentli ve NBD'li hastalarda taburculuk sonrası takip sürelerinin, NBD'li hastalarda anlamlı olarak kısa olduğu gösterilmiştir. Çalışmamız uygulanacak modalitenin belirlenmesinde kaçak yerinin de göz önüne alınması gerektiğini düşündürmektedir. Hastanede yatış süresi daha uzun olan 2. grupta (tip A dışı), hospitalizasyon süresi daha az olan biliyer stentin tercih edilmesinin daha uygun olabileceğini düşündürmektedir.

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Does COVID-19 Infection Pose a Risk to Women of Childbearing Age?

COVID-19 Enfeksiyonu Doğurganlık Çağındaki Kadınlar için Risk Oluşturur mu?

Kazım KIRATLI [1*], Mustafa SENGUL [2]

[1] Katip Celebi University Ataturk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey
[2] Katip Celebi University Ataturk Training and Research Hospital, Department of Gynecology and Obstetrics, Izmir, Turkey

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Abstract

Objective: This study aims to investigate the potential differential impact of COVID-19 infection on pregnant women compared to non-pregnant individuals of childbearing age by evaluating laboratory findings from both inpatient and outpatient cases.

Material and Methods: From the onset of COVID-19 in Turkey in March 2020 until the commencement of vaccination, a total of 94 COVID-19 patients were included in three separate groups: pregnant women and non-pregnant individuals with COVID-19 (with and without pneumonia). Sociodemographic data and examination findings were retrospectively retrieved from the hospital information system.

Results: The study revealed that pregnant women, with a mean age of 28.87±1.38, experienced a significantly shorter mean length of hospital stay of 5.03±0.49 days compared to the other groups ($p<0.001$). Notably, pregnant women exhibited significant variations in urea, creatinine, white blood cell count, neutrophil count, hemoglobin, and hematocrit values in comparison to the other groups ($p<0.001$). Moreover, there were significant differences among the three groups concerning neutrophil and lymphocyte percentage values ($p<0.001$).

Conclusion: The study suggests that COVID-19 infection in pregnant women is associated with more favorable clinical outcomes, shorter length of hospital stay, and relatively moderate alterations in laboratory findings when accounting for pregnancy-induced changes. It is implied that pregnancy might not pose as substantial a risk factor for severe COVID-19 infection as advanced age or underlying chronic conditions such as diabetes, asthma, COPD, and malignancy.

Keywords: COVID-19; Infection; Pregnancy; Pneumonia

Özet

Amaç: Bu çalışma, hem yatan hem de ayakta tedavi vakalarından elde edilen laboratuvar bulgularını değerlendirerek, çocuk doğurma çağındaki hamile olmayan bireylerle karşılaştırıldığında, COVID-19 enfeksiyonunun hamile kadınlar üzerindeki potansiyel farklı etkisini araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Türkiye'de COVID-19'un ortaya çıktığı Mart 2020'den aşılamanın başlamasına kadar toplam 94 COVID-19 hastası üç ayrı gruba dahil edildi: hamile kadınlar ve hamile olmayan COVID-19'lu bireyler (pnömonisi olan ve olmayanlar) . Sosyodemografik veriler ve muayene bulguları hastane bilgi sisteminden geriye dönük olarak elde edildi.

Bulgular: Araştırmada yaş ortalaması 28,87±1,38 olan gebelerin diğer gruplara göre anlamlı olarak daha kısa ortalama hastanede kalış süresi (5,03±0,49 gün) yaşadığı ortaya çıktı ($p<0,001$). Özellikle gebelerde üre, kreatinin, beyaz küre sayısı, nötrofil sayısı, hemoglobin ve hematokrit değerlerinde diğer gruplara göre anlamlı farklılıklar görüldü ($p<0,001$). Ayrıca nötrofil ve lenfosit yüzde değerleri açısından da üç grup arasında anlamlı fark vardı ($p<0,001$).

Sonuç: Çalışma, hamile kadınlarda COVID-19 enfeksiyonunun, hamileliğin neden olduğu değişiklikler hesaba katıldığında daha olumlu klinik sonuçlar, daha kısa hastanede kalış süresi ve laboratuvar bulgularında nispeten orta düzeyde değişikliklerle ilişkili olduğunu öne sürüyor. Gebeliğin ciddi COVID-19 enfeksiyonu açısından ileri yaş veya diyabet, astım, KOAH ve malignite gibi altta yatan kronik durumlar kadar önemli bir risk faktörü oluşturmayabileceği düşünülmektedir.

Anahtar Kelimeler: Covid-19, Enfeksiyon, Gebelik, Pnömoni

***Sorumlu Yazar/Corresponding Author:** Kazım KIRATLI, Katip Celebi University Ataturk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey. **E-mail:** drkazimkiratli@gmail.com

INTRODUCTION

The emergence of the COVID-19 pandemic can be traced back to December 29, 2019, when four cases of pneumonia with an unidentified origin were identified in Wuhan, the capital of China's Hubei province. Subsequent whole genome sequencing of the oropharynx and nasal samples from these cases on January 12, 2020, revealed the presence of a previously undiscovered coronavirus (CoV) strain. On February 11, 2020, the International Committee on Virus Taxonomy named it "Severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2), and the World Health Organization (WHO) designated the resulting disease as COVID-19 [1]. SARS-CoV-2 is primarily transmitted through inhalation of droplets expelled into the environment by infected individuals through coughing or sneezing. Alternatively, transmission can occur by touching contaminated surfaces and subsequently introducing the virus into the body through the mouth or nose [2,3]. The genetic similarity of SARS-CoV-2 to other coronaviruses such as severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) (79%) and Middle East respiratory syndrome coronavirus (MERS) (50%) places it within the same group. Coronaviruses, a class of enveloped, positive single-stranded RNA viruses, can present with a spectrum of illnesses, spanning from common cold symptoms to severe pneumonia and fatality [4].

Upon entering a host, SARS-CoV-2 initially attaches to cell receptors and gains entry by means of fusion. Following this, the viral RNA penetrates the cell nucleus for replication, utilizing viral mRNA to synthesize viral proteins in a process known as biosynthesis. Subsequently, newly formed viral particles are enclosed in vesicles, transported to the cell membrane, and eventually released [5,6].

A notable observation is the heightened expression and activity of angiotensin-converting enzyme 2 (ACE-2), a key receptor for SARS-CoV-2, in the uterus, kidney, and placenta during pregnancy. Consequently, these reproductive organs are considered prime targets for SARS-CoV-2 infection [7]. The severity of symptoms, such as hypoxia and pneumonia, is thought to be correlated with increased ACE-2 expression [8]. Transmembrane ACE-2 enzymes are also found in various other tissues, including enterocytes, type II alveolar cells, smooth muscles, vascular endothelial tissue, and certain neurons [9].

Pregnant women faced high mortality rates during past significant pandemics such as the 1918 Spanish influenza (27-50% mortality), SARS-CoV-1 (25-30% mortality), and MERS (~40% mortality) [2,3]. In the more recent H1N1 pandemic, pregnant and perinatal mortality rates

surpassed those of the general population [10]. There is a growing body of evidence suggesting that complications like miscarriage, intrauterine and neonatal deaths, preterm births, and preeclampsia are on the rise with the spread of COVID-19 [11]. Pregnancy-related immunological and physiological changes, including increased oxygen demand, shifts in T lymphocyte immunity, and decreased functional residual capacity, render pregnant individuals more vulnerable to respiratory pathogens, leading to elevated maternal and fetal risks [12]. Irrespective of pregnancy, COVID-19 exhibits a more severe course in the elderly (above 65 years old) and individuals with underlying chronic conditions like diabetes, obesity, kidney disease, heart disease, lung disease, and cancer, independent of age [13]. Studies investigating laboratory findings among COVID-19 patients have reported changes in parameters such as whole blood composition, liver enzymes, albumin, creatine kinase (CK), ferritin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and D-dimer levels [14].

Given the swift global spread of COVID-19, its recent discovery, the absence of definitive treatment, and the historical vulnerability of pregnant women in pandemics, concerns for pregnant women and fetuses have intensified. The aim of this study was to meticulously assess clinical and laboratory data from both pregnant and non-pregnant female patients with COVID-19 who were monitored as both inpatients and outpatients, as well as to discern whether the disease's impact on pregnancy differs from its effects on non-pregnant individuals.

METHODS

In our study, a total of 94 COVID-19 patients were divided into 3 separate groups and analyzed: 1st group: 31 patients (pregnant women), 2nd group: 30 patients (non-pregnant, pneumonia +), 3rd group: 33 patients (non-pregnant, pneumonia -). The non-pregnant patients consisted of women of reproductive age. The study's first group consisted of all pregnant cases (31 patients) who underwent follow-up at our clinic between March 2020, when Turkey's Covid-19 outbreak began, and January 2021, when the nation's first vaccination program was implemented. The patients in the other two non-pregnant groups were drawn at random and similar numbers from patients of reproductive age who were under treatment for the same period of time. Individuals with any comorbidities that may affect the course of Covid-19 are not present in the study groups. This research was planned retrospectively, sociodemographic characteristics, clinical manifestations, and findings from examinations and imaging studies were extracted from the hospital information management system.

To identify and isolate individuals infected with SARS-CoV-2, we employed PCR testing utilizing the Bio-speedy SARS-Cov-2 real-time polymerase chain reaction (Rt-PCR) detection kit developed by Bioksen in Istanbul, Turkey. This diagnostic procedure was performed on samples collected from nasopharyngeal swabs obtained from the patients.

Ethical Approval

The research was approved by the Ministry of Health for Scientific Research and Izmir Katip Celebi University (İKCÜ) Ethics Committee (Ministry of Health Scientific Research Form No: 2021-04-18T17_42_00) (İKCÜ Non-Invasive Clinical Research Ethics Committee Decision Form: 0244/29.04.2021).

Statistical Analysis

The statistical analysis of the study data was conducted using the SPSS version 21.0 (Statistical Package for the Social Sciences) software. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For group comparisons, the ANOVA test with post hoc Bonferroni correction was employed for continuous variables conforming to normal distribution, while the Kruskal-Wallis test was utilized for continuous variables not conforming to normal distribution. All measurements are presented as "mean ± standard error." A significance level of $p<0.05$ was considered as the threshold for significance.

RESULTS

The mean age of the pregnant women included in the study was 28.87±1.38 years. Their mean length of hospital stay was 5.03±0.49 days, which significantly differed from the other groups ($p<0.001$) (Table 1). Pregnant and non-pregnant adult patients exhibited similar rates of COVID-19 symptoms. The most common symptom in both groups was fever (pregnant: 73.3%; non-pregnant: 71.6%), followed by cough (pregnant: 53.3%; non-pregnant: 63.3%), and headache (pregnant: 43.3%; non-pregnant: 46.6%). Additional common symptoms included myalgia (30%) and chills (26.6%) in pregnant women, as well as a reduced sense of taste/smell (35%) and fatigue (26.6%) in non-pregnant patients. Other frequent symptoms are detailed in Table 2.

Significant differences were observed between pregnant women and the other groups concerning urea and creatinine values ($p<0.001$). Furthermore, LDH values were notably higher in the pneumonia group compared to the other two groups ($p<0.001$). Pregnant patients and those with pneumonia displayed elevated CRP, ferritin, ESR, and D-dimer values (Table 1).

Table 1- Length of Hospital Stay, Mean Age and Biochemical Parameters of the Patients

Parameters	Pregnant patients	Non-Pregnant Pneumonia (+)	Non-Pregnant Pneumonia (-)	p
Age	28.87±1.38[a*]	36.79±1.30[b]	33.57±1.43[b]	<0.001
Hospitalization Period (day)	5.03±0.49[a]	10.17±0.65[b]	9.31±0.59[b]	<0.001
Ure	6.87±0.43[a]	9.76±0.51[b]	9.46±0.42[b]	<0.001
Creatinine	0.60±0.02[a]	0.74±0.02[b]	0.69±0.01[b]	<0.001
AST	22.37±2.36[a]	28.03±3.57[a]	21.51±3.06[a]	0.272
ALT	18.86±3.77[a]	38.20±9.40[a]	25.59±6.82[a]	0.162
LDH	168.20±11.64[a]	219.10±13.67[b]	147.03±7.77[a]	<0.001
CK	84.13±8.50[a]	74.00±12.81[a]	79.29±8.60[a]	0.785
CRP	25.53±5.79[ab]	49.67±13.69[b]	9.43±4.41[a]	0.005
D-dimer	1025.67±322.94[a]	542.52±212.52[ab]	157.31±21.86[b]	0.016
Ferritin	83.97±10.52[ab]	141.83±27.62[b]	60.49±14.53[a]	0.008
Procalcitonin	0.08±0.01[a]	0.10±0.03[a]	0.11±0.08[a]	0.930
ESR	30.97±4.59[a]	36.03±3.90[a]	15.63±2.64[b]	<0.001

* Different letters indicate statistical significance.

Table 2- Distribution of Symptoms

Symptoms	Pregnants	Non- pregnants
Fever	%73.3	%71.6
Cough	%53.3	%63.3
Headache	%43.3	%46.6
Myalgia	%30	%23.3
Chills	%26.6	%21.6
Loss of taste/smell	%23.3	%35
Fatigue/Weakness	%20	%26.6
Dyspnea	%16.6	%25
Nausea/Vomiting	%13.3	%16.6
Sore throat/runny nose	%6.6	%8.3
Diarrhea	%3.3	%3.3

In terms of WBC count, neutrophil count, hemoglobin, and hematocrit values, there were significant differences between pregnant women and the other groups ($p<0.001$). Moreover, significant differences emerged among the three groups in terms of neutrophil and lymphocyte percentage values ($p<0.001$), while no differences were observed between the three groups concerning lymphocyte and platelet counts ($p>0.05$) (Table 3).

Table 3- Complete Blood Parameters of the Patients

Parameters	Pregnant patients	Non-Pregnant Pneumonia (+)	Non-Pregnant Pneumonia (-)	p
WBC	10.43 ± 0.56^{a}	6.62 ± 0.73^{b}	5.79 ± 0.55^{b}	<0.001
NEU	7.93 ± 0.52^{a}	4.52 ± 0.72^{b}	3.41 ± 0.47^{b}	<0.001
NEU %	74.58 ± 1.51^{a}	64.74 ± 1.90^{b}	53.23 ± 2.47^{c}	<0.001
LYM	1.77 ± 0.10^{a}	1.52 ± 0.10^{a}	1.72 ± 0.09^{a}	0.178
LYM %	18.02 ± 1.20^{a}	26.05 ± 1.84^{b}	34.77 ± 2.14^{c}	<0.001

MONO	0.63±0.03[a]	0.48±0.04[a]	0.57±0.06[a]	0.078
MONO %	6.44±0.47[a]	7.78±0.54[a]	10.02±0.61[b]	<0.001
RBC	3.94±0.08[a]	4.58±0.08[b]	4.56±0.07[b]	<0.001
HGB	11.28±0.25[a]	12.54±0.29[b]	12.65±0.23[b]	<0.001
HCT	32.89±0.58[a]	37.87±0.66[b]	38.15±0.53[b]	<0.001
PDW	12.64±0.56[a]	11.98±0.34[a]	12.35±0.34[a]	0.555
RDW	14.14±0.59[a]	13.64±0.29[a]	13.59±0.29[a]	0.583
PLT	230.90±14.06[a]	252.41±15.42[a]	237.17±12.43[a]	0.551
PCT	0.26±0.02[a]	0.26±0.01[a]	0.25±0.01[a]	0.840

* Different letters indicate statistical significance.

The analysis of obstetric characteristics revealed that the highest number of pregnancies (gravida) was 2 (46.7% - n:14), with the maximum parity number being 1 (56.7% - n:17). The cesarean delivery rate was 56.7% (n:17), and the rate of premature births (<37 weeks) stood at 26.7% (n:8). The mean fetal weight was recorded as 3048 g (Table 4).

Table 4- Obstetrical Characteristics

Gravida	Parity	Birth week	Fetal growth retardation (<2500 g)	Type of birth (Cesarean section)	Mean fetus weight (g)	Mean postpartum Hgb (After 6 hours)
1.9±0.9 (1-5)	1.0±0.8 (0-4)	38.2±1.8 (35-40)	%26.7 (n:8)	%56.7 (n:17)	3048.3±472.2 (2040-4250)	10.1±1.5 (7.6-13.5)

DISCUSSION

Physiological changes inherent to pregnancy, such as a reduction in anticoagulant factors coupled with an elevation in procoagulant factors, result in a hypercoagulable state, leading to an increase in D-dimer levels [15]. Concurrently, adverse outcomes like preterm labor, low birth weight infants, decreased Apgar scores, and occurrences of preeclampsia/eclampsia are more prevalent among pregnant women with pneumonia [16]. Coagulation disturbances noted in COVID-19 non-pregnant patients are linked to poorer

prognoses, prompting concerns that the pre-existing pregnancy-related coagulopathy could amplify the morbidity and mortality associated with COVID-19 [17].

Among the general population, the most common COVID-19 symptoms include cough, fever, myalgia, fatigue, headache, and shortness of breath, respectively [18]. Pregnant women similarly experience SARS-CoV-2 symptoms, with fever and cough being predominant, and the severity parallels that in non-pregnant counterparts [19-21]. In our study, comparable rates of fever, cough, and headache were the most prevalent symptoms in both groups.

A comprehensive meta-analysis involving 26 studies (including 11,580 women) focused on pregnant individuals with suspected or confirmed COVID-19 infection. This analysis revealed that a severe form of the disease was observed in 6-21% of patients (mean 13%), with 2-7% requiring intensive care unit (ICU) admission (mean 4%), 1-5% needing mechanical ventilation (mean 3%), and 0.4% necessitating extracorporeal membrane oxygenation. Concurrent maternal comorbidities such as chronic hypertension, advancing maternal age, high body mass index, and diabetes were identified as risk factors for a severe disease course [22]. A Chinese study of hospitalized pregnant women with COVID-19 reported that 77% experienced fever and 23% exhibited shortness of breath. Within this cohort, 46% delivered prematurely between weeks 32-36 of gestation. Remarkably, 23% responded positively to treatment and were discharged to resume their pregnancies. Severe pneumonia and multi-organ dysfunction requiring ICU care and extracorporeal membrane oxygenation were noted in 7.6% of cases [23]. Another meta-analysis confirmed that pregnant women with COVID-19 manifested similar symptoms and experienced comparable disease severity as the broader adult population [24]. A study on pregnant women with COVID-19 pneumonia highlighted that the ICU admission rate resembled that of non-pregnant women. However, rates of preterm labor and cesarean delivery were higher compared to pregnant women without COVID-19 [25]. In our study, the cesarean section rate reached 56.7%, while preterm delivery and low birth weight incidence were found as 26.7%.

In a study by Liu et al. [26], 85% of patients exhibited elevated LDH and CRP levels, while 15% had leukocytosis and 43% experienced lymphopenia. Neutrophil counts were elevated in 57% of cases, whereas platelet counts remained within the normal range for all patients. Furthermore, 85%, 72%, and 85% of patients showed normal procalcitonin, ALT, and AST levels, respectively. However, low albumin levels were noted in 43% of patients. Another study reported a higher prevalence of leukocytosis and elevated neutrophil ratios in pregnant individuals infected with COVID-19. Nonetheless, no notable difference emerged between

pregnant and non-pregnant groups in terms of lymphopenia. Elevated CRP levels were consistently observed in a majority of cases [27]. In a larger study including COVID-19 patients, common laboratory findings encompassed increased CRP (73.6%), decreased albumin (62.9%), elevated ESR (61.2%), decreased eosinophil counts (58.4%), lymphopenia (47.9%), and increased LDH levels (46.2%) [28]. Xie et al. [29] identified lymphopenia, leukopenia, elevated CRP, ferritin, and LDH as prominent laboratory findings among COVID-19 patients. Similarly, in another study on pregnant women, the most frequent laboratory findings were increased neutrophil counts, lymphopenia, and elevated CRP values. While the rate of leukocytosis and thrombocytopenia was higher in pregnant women, the percentage of elevated CRP was lower compared to non-pregnant individuals. D-dimer levels were elevated in both groups, but notably higher in pregnant women. Lymphopenia and elevated CRP were recurrent findings in meta-analyses of other pregnant patients [20]. In our study, LDH values were elevated in the pneumonia group compared to the other two groups, while CRP, ferritin, D-dimer, and ESR values were higher in pregnant patients and those with pneumonia. Notably, significant neutropenia was observed in non-pregnant patients, and hemoglobin levels were lower in pregnant patients. Thrombocytopenia and lymphopenia displayed similar patterns between the groups.

In another study focused on pregnant women, the results revealed that markers such as neutrophils, WBC count, procalcitonin, CRP, and D-dimer were notably elevated in pregnant individuals. Additionally, the mean lymphocyte percentage was lower compared to non-pregnant women [30].

It is important to acknowledge several limitations in our study. The exclusive inclusion of pregnant women in their last trimester might not comprehensively capture the virus's impact during the 1st and 2nd trimesters. Moreover, the study does not provide insight into the long-term effects on both pregnant women and fetuses. The study's relatively small sample size and the fact that it was conducted before vaccination are additional limitations that need to be considered. Although the higher average age of nonpregnant women in each group may be considered a limitation, randomization may also suggest that nonpregnant women of childbearing age may be reluctant to seek medical care when they first show symptoms.

CONCLUSION

This study attempted to elucidate the trajectory of COVID-19 in pregnant patients compared to the non-pregnant adult population. Given past experiences with severe respiratory illnesses,

initial assumptions suggested that SARS-CoV-2 might disproportionately impact pregnant women. However, the majority of data point to relatively lower rates of maternal morbidity and mortality in comparison to prior coronavirus pandemics. The study revealed a more favorable disease course among pregnant women, characterized by shorter length of hospital stay and moderate alterations in laboratory parameters (taking pregnancy-related changes into account). These results indicate that, when considering factors like age and underlying health conditions, pregnancy might not pose as a serious risk for COVID-19 as advanced age or chronic illnesses such as diabetes, asthma, COPD, and malignancy. Considering the known associations between being female and younger age with improved COVID-19 outcomes, it is likely that this group would exhibit lower morbidity and mortality rates within the general population. However, the observation of increased rates of low birth weight, cesarean section, and preterm births in pregnant women with COVID-19 raises concerns about potential correlations between the disease and pregnancy complications. While our study provides valuable insights, the long-term effects of COVID-19 on fetuses and newborns remain uncertain. Further studies are needed for enhancing our understanding of pregnancy management during illness.

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Authorship Contributions: Concept – KK, MS; Design – KK, MS; Data Collection and/or Processing – KK, MS; Analysis and/or Interpretation – KK, MS; Literature Review – KK, MS; Writing – KK.

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Modeling and Forecasting COVID-19 Incidence Rates: A Time Series Analysis of Acute Respiratory Infections (ARI) in France Since Surveillance Initiation

COVID-19 İnsidans Oranlarını Modelleme ve Öngörümleme: Fransa'da Gözetim Başlangıcından Beri Akut Solunum Enfeksiyonları (ASE) Zaman Serisi Analizi

Hanife TAYLAN SELAMLAR*
*Department of Statistics, Faculty of Science, Dokuz Eylül University, İzmir, Turkey

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Abstract

Objective: This study aims to address the challenges of planning and managing the trajectory of the COVID-19 pandemic by evaluating the predictive abilities of three distinct forecasting models. The primary focus is on the ATA univariate forecasting method, ARIMA (AutoRegressive Integrated Moving Average), and ETS (Error-Trend-Seasonality) models. These models are applied to a meticulously collected dataset comprising Acute Respiratory Infections (ARI) incidence rates in France, systematically collected since the initiation of surveillance.

Methods: The purpose of the study was to conduct a comprehensive evaluation of forecasting models using the selected dataset to achieve its objective. The focus was on comparing the accuracy and performance of ATA univariate forecasting, ARIMA, and ETS models in predicting COVID-19 incidence rates. Additionally, the study incorporated a combination approach proven to be effective in enhancing forecasting performance.

Results: According to the results obtained regarding forecast performance, the univariate models indicate that the ATA method exhibits the highest performance, while observations reveal that combinations of ATA and ARIMA methods enhance forecast accuracy.

Conclusions: In summary, the most accurate approach for forecasting future Covid-19 incidence rates, specifically those derived from Acute Respiratory Infections (ARI), has been a combination of the high-accuracy methods ATA and ARIMA. These findings enhance our understanding of the trajectory of the pandemic, providing a foundation for strategic planning and effective management.

Keywords: Covid-19, ATAforecasting, ETS, ARIMA, Acute Respiratory Infections (ARI)

Özet

Amaç: Bu çalışma, COVID-19 pandemisinin gidişatını planlama ve yönetme zorluklarına karşı üç farklı tahmin modelinin öngörü yeteneklerini değerlendirerek ele almayı amaçlamaktadır. Temel odak noktası, ATA tek değişkenli tahmin yöntemi, ARIMA (OtoRegresif Entegre Hareketli Ortalama) ve ETS (Hata-Eğilim-Mevsimlilik) modelleridir. Bu modeller, Fransa'da gözetimin başlangıcından bu yana titizlikle toplanan Akut Solunum Enfeksiyonları (ASE) insidans oranlarını içeren bir veri setine uygulanmıştır.

Yöntem: Çalışmanın amacına ulaşmak için seçilen veri setini kullanarak tahmin modellerinin kapsamlı bir değerlendirmesini yapmak amaçlanmıştır. Odak noktası, COVID-19 insidans oranlarını tahmin etmede ATA tek değişkenli tahmin, ARIMA ve ETS modellerinin doğruluğunu ve performansını karşılaştırmaktır. Ayrıca, çalışma, tahmin performansını artırmada etkili olduğu kanıtlanmış bir kombinasyon yaklaşımını da içermiştir.

Bulgular: Tahmin performansına ilişkin elde edilen sonuçlara göre, tek değişkenli modeller, ATA yönteminin en yüksek performansı sergilediğini gösterirken gözlemler, ATA ve ARIMA yöntemlerinin kombinasyonlarının tahmin doğruluğunu artırdığını göstermektedir.

Sonuç: Özetle, gelecekteki Covid-19 insidans oranlarını, özellikle Akut Solunum Enfeksiyonları (ASE) kaynaklı olanları tahmin etmede en doğru yaklaşım, ATA ve ARIMA gibi yüksek doğrulukta yöntemlerin kombinasyonu olmuştur. Bu bulgular, pandeminin seyrine dair anlayışımızı artırarak stratejik planlama ve etkili yönetim için bir temel sağlamaktadır.

Anahtar Kelimeler: Covid-19, ATA, ETS, ARIMA, Akut Solunum Enfeksiyonları (ASE)

***Sorumlu Yazar / Corresponding Author:** Department of Statistics, Faculty of Science, Dokuz Eylül University, İzmir, Turkey. **E-mail**: hanife.taylan@deu.edu.tr

INTRODUCTION

The ongoing COVID-19 pandemic has emphasized the need for robust modeling techniques to understand its trajectory and make informed predictions. In this study, we explore the application of ATA forecasting method, ARIMA (AutoRegressive Integrated Moving Average), and ETS (Error-Trend-Seasonality) models to systematically collected Acute Respiratory Infections (ARI) incidence rates in France since the initiation of surveillance. The objective is to evaluate the forecasting capabilities of these models in estimating COVID-19 incidence rates. Effective forecasting models are essential for strategic planning and effective management of public health crises. By comparing the forecast performances of these models with actual data, this study aims to contribute valuable insights into predicting future incidence rates and enhancing our understanding of the evolving dynamics of the COVID-19 pandemic.

To enhance our understanding of forecasting methodologies, let's begin with a review of the ATA forecasting method. ATA, a straightforward and accurate statistical method, optimizes smoothing parameters and initial values simultaneously through a weighted approach based on the number of observations. Previous research has demonstrated its efficacy in improving forecast accuracy, outperforming alternatives, and showcasing superior performance in various datasets. This study proposes the Modified Simple Exponential Smoothing (MSES) method as an improved alternative to Simple Exponential Smoothing (SES), addressing its limitations for enhanced forecast accuracy, particularly evident in the M-competition's 1001 time series data [1].

In addressing the failures of Simple Exponential Smoothing, [2] compares the Ata-Simple exponential smoothing method to the standard SES. The analysis provides insights into the reasons for the failures of exponential smoothing and offers a comparative assessment of their accuracy in various forecasting scenarios. [3] introduces a modification to Holt's Linear Trend method for time series forecasting, exploring its impact on accuracy and potential advantages in capturing trends.

Introducing the ATA method for time series forecasting, [4] focuses on the additive ATA model with a linear trend component. The study highlights the single model's ability to rival alternative methods, emphasizing the substantial potential of the ATA approach.

[5] compares the ATA method to Croston-based methods for forecasting intermittent demand, and [6, 7] conducts a comparison between ATA and exponential smoothing methods on datasets with or without linear trends, demonstrating the superior performance of the proposed approach. [8] introduces an automatic time series forecasting using the ATA method, automating various stages for enhanced accessibility and simplifying the forecasting process. The fable.ata R

package serves as a modeling interface between ATAforecasting and fable, facilitating time series analysis and forecasting within the fable framework.

While ARIMA and ETS models are well-established for time series analysis, their effectiveness in modeling COVID-19 incidence rates has been explored extensively. In comparing exponential smoothing and ARIMA models, the ARIMA (0,0,2) model proves optimal for short-duration data, whereas the Holt-Winters Exponential Smoothing model exhibits greater accuracy for longer time series datasets [9]. Notably, advancements in ARIMA modeling, as exemplified by the ARIMAI model, showcase enhanced accuracy and efficiency, surpassing the capabilities of traditional ARIMA models [10].

Further contributions to the field include the development of an optimized EVDHM-ARIMA model tailored for COVID-19 forecasting, aiming to detect virus transmission rates and predict infection instances [11]. The exploration of combined approaches, such as ARIMA and ARM techniques, surfaces as a valuable strategy for COVID-19 forecasting, with the ARIMAX model incorporating ARM factors demonstrating superior predictive performance [12].

This study, in its broader scope, seeks to propose the most effective model for forecasting COVID-19 cases, shedding light on the diverse methodologies employed in recent research efforts. The evaluation of models extends to the ETS model, highlighted for its minimal Mean Absolute Percentage Error (MAPE) statistics when compared to other models [13]. The synthesis of these findings aims to provide a comprehensive understanding of the evolving landscape of COVID-19 forecasting methodologies.

Extending this methodology to France, time series analysis of ARI data has been instrumental in modeling and forecasting COVID-19 incidence rates. This comprehensive approach aims to contribute not only to accurate forecasts but also to a deeper understanding of the multifaceted dynamics surrounding COVID-19 incidence rates.

METHODS

Univariate Forecasting Method of ATA

The ATA method is an innovative forecasting technique that incorporates forms similar to exponential smoothing models. What sets ATA apart is its adaptive approach, where smoothing parameters dynamically adapt to sample size. Unlike traditional methods, ATA optimizes parameters in a discrete space, simplifying initialization. The simultaneous optimization and initialization process, with rapidly approaching zero weights for initial values, make ATA less influential, ensuring robust forecasting. ATA's universal applicability to all time series settings

offers superior forecasting performance due to its inherent flexibility. In this study, the ATA method was applied to health-related data, demonstrating its positive performance and potential for broader application domains. The following paragraphs will explain the intricacies of the ATA method, including its formula and application nuances.

For a time series $\{\mathbf{y_1}, \dots, \mathbf{y_n}\}$ ATA method can be given in additive form as below:

$$\mathbf{l_t} = \left(\frac{\mathbf{p}}{\mathbf{t}}\right)\mathbf{y_t} + \left(\frac{\mathbf{t-p}}{\mathbf{t}}\right)(\mathbf{l_{t-1}} + \emptyset\mathbf{b_{t-1}}), \tag{1.1}$$

$$\mathbf{b_t} = \left(\frac{\mathbf{q}}{\mathbf{t}}\right)(\mathbf{l_t} - \mathbf{l_{t-1}}) + \left(\frac{\mathbf{t-q}}{\mathbf{t}}\right)(\emptyset\mathbf{b_{t-1}}), \tag{1.2}$$

where p is the smoothing parameter for level, q is the smoothing parameter for trend, $\emptyset$ is the dampening parameter and $l_t = y_t$ for $t \leq p$, $b_t = y_t - y_{t-1}$ for $t \leq q$, $b_1 = 0$, $p \in \{1,2, \dots, n\}$, $q \in \{0,1,2, \dots, p\}$, $\emptyset \in (0,1]$. Then, the h step ahead forecasts can be obtained by:

$$\hat{\mathbf{y}}_{\mathbf{t+h|t}} = \mathbf{l_t} + \left(\emptyset + \emptyset^{\mathbf{2}} + \cdots + \emptyset^{\mathbf{h}}\right)\mathbf{b_t}. \tag{1.3}$$

Similarly for a time series $\{y_1, \dots, y_n\}$ ATA method can be given in multiplicative form as below:

$$l_t = \left(\frac{p}{t}\right)y_t + \left(\frac{t-p}{t}\right)\left(l_{t-1}b_{t-1}^{\emptyset}\right), \tag{2.1}$$

$$\mathbf{b_t} = \left(\frac{\mathbf{q}}{\mathbf{t}}\right)\left(\frac{\mathbf{l_t}}{\mathbf{l_{t-1}}}\right) + \left(\frac{\mathbf{t-q}}{\mathbf{t}}\right)\left(\mathbf{b_{t-1}^{\emptyset}}\right), \tag{2.2}$$

where again p is the smoothing parameter for level, q is the smoothing parameter for trend, $\emptyset$ is the dampening parameter and $l_t = y_t$ for $t \leq p$, $b_t = \frac{y_t}{y_{t-1}}$ for $t \leq q$, $b_1 = 1$, $p \in \{1,2, \dots, n\}$, $q \in \{0,1,2, \dots, p\}, \emptyset \in (0,1]$. Then, the h step ahead forecasts can be obtained by:

$$\hat{\mathbf{y}}_{\mathbf{t+h|t}} = \mathbf{l_t} + \mathbf{b_t^{\left(\emptyset+\emptyset^{2}+\cdots+\emptyset^{h}\right)}}. \tag{2.3}$$

Since both versions of the method require three parameters we will distinguish between them by using the notation $\mathrm{ATA}_{\mathrm{add}}(p, q, \emptyset)$ for the additive form and $\mathrm{ATA}_{\mathrm{mult}}(p, q, \emptyset)$ for the multiplicative form.

Notice that when $q = 0$ both forms of ATA are reduced to the simple form $\mathrm{ATA}(p, 0, \emptyset)$ which can be written as:

$$l_t = \left(\frac{p}{t}\right)y_t + \left(\frac{t-p}{t}\right)l_{t-1}, \tag{3.1}$$

where $\mathbf{p} \in \{\mathbf{1}, \mathbf{2}, \dots, \mathbf{n}\}$ and $\mathbf{l_t} = \mathbf{y_t}$ for $\mathbf{t} \leq \mathbf{p}$. Forecasts then can be obtained by $\hat{\mathbf{y}}_{\mathbf{t+h|t}} = \mathbf{l_t}$.

To sum up, ATA can be given in different forms, namely the additive damped form $\mathrm{ATA}_{\mathrm{add}}(\mathrm{p}, \mathrm{q}, \emptyset)$ (equations (1.1)-(1.3)), multiplicative damped form $\mathrm{ATA}_{\mathrm{mult}}(\mathrm{p}, \mathrm{q}, \emptyset)$ (equations (2.1)-(2.3)), simple form $\mathrm{ATA}(\mathrm{p}, 0, \emptyset)$ (equation (3.1)).

ARIMA Model

The AutoRegressive Integrated Moving Average (ARIMA) model is widely used in time series analysis [14]. ARIMA assesses the relationships and trends between previous values of the existing data. The model combines three essential components: AutoRegressive (AR), Integrated (I), and Moving Average (MA) [15]. The AutoRegressive component represents the relationship between past values, while the Moving Average predicts future values through the current error terms. The Integration component determines the stationarity level in the data series [16]. By combining these components, the ARIMA model provides a robust tool for understanding time series data and predicting future values.

ETS Model

The Error-Trend-Seasonality (ETS) model is a forecasting model that takes errors, trends, and seasonality into account when making predictions [16]. The ETS model combines three fundamental components: error, trend, and seasonality [17]. The error component represents the difference between predictions and actual values. The trend component determines the overall trend in the data set. The seasonality component describes repeated patterns in a specific period [18]. By integrating these three components, the ETS model effectively analyzes time series data and predicts future values.

Modeling and Forecasting

In this study, ATA, ARIMA, and ETS forecasting methods were applied to a meticulously collected dataset of Acute Respiratory Infections (ARI) incidence rates in France since the initiation of surveillance. The weekly time series dataset, spanning from 2020 to 2023, captures the temporal dynamics of ARI, providing a rich source for modeling and forecasting the incidence rates of these respiratory infections, as illustrated in Figure 1. Each entry in the dataset corresponds to a specific time point, allowing for a comprehensive exploration of the temporal patterns and trends associated with ARI. For this exploration, the dataset was divided into test and train sets, with the last year, consisting of 52 weeks, designated as the test data. The relevant models were trained on the training portion and their performances were compared using the

test data. Based on this comparison, the best-performing model, i.e., the one with the highest forecast accuracy, was used to predict the first 13 weeks of 2024.

The ARI dataset encompasses a variety of information, including regularly recorded incidence rates, potential influencing factors, and the contextual backdrop of public health interventions. The graph below illustrates instances where incidence rates show increases at specific time intervals in the given dataset. This study aims to obtain the most accurate time series method for predicting the first 13 weeks of the year 2024.

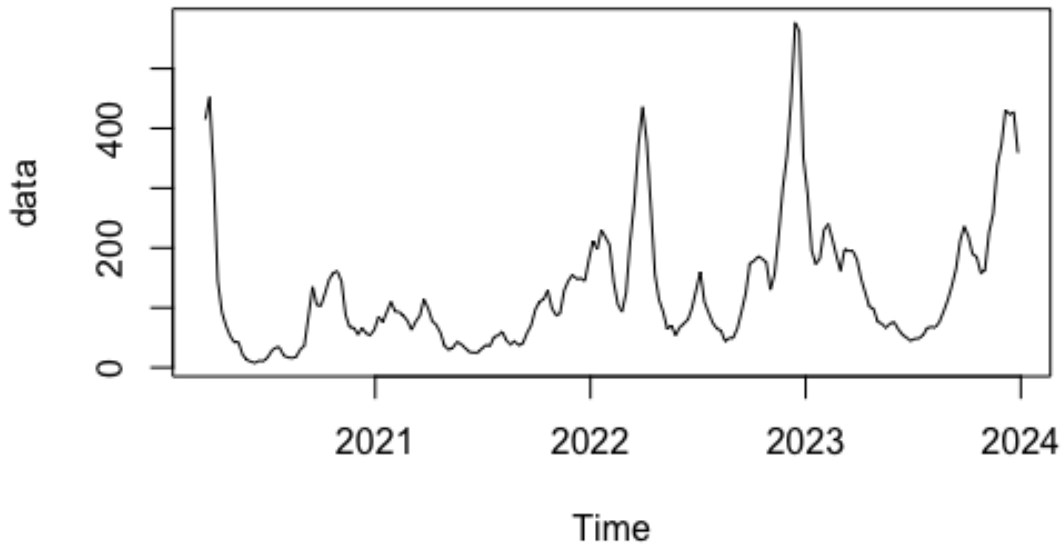

Figure 1. Incidence rate of acute respiratory infection (ARI) in France from start of surveillance (Rate per 100 000 inhabitants)

RESULTS

Table 1 illustrates the accuracy performance of the employed forecasting methods, namely ATA, ETS, and ARIMA, across various accuracy measures. Root Mean Square Error (RMSE) is a metric used to quantify the average magnitude of errors between forecasted and observed values. It is particularly useful as it squares the errors, giving more weight to larger discrepancies. On the other hand, Mean Absolute Error (MAE) provides a straightforward measure by calculating the average absolute differences between forecasted and observed values, offering insight into overall accuracy without emphasizing the size of errors.

Mean Percentage Error (MPE) takes a step further by expressing the average percentage difference between forecasted and observed values. This metric provides information on the direction and magnitude of errors, giving a sense of the overall accuracy of the model in a percentage format. Complementing this, Mean Absolute Percentage Error (MAPE) calculates the average absolute percentage differences, offering a relative measure of accuracy that is easy to interpret.

Lastly, Mean Absolute Scaled Error (MASE) compares the forecasting model's performance to a naive model, taking into account both the scale and direction of errors. This metric is valuable for assessing how well the model performs in relation to a baseline, providing a comprehensive evaluation of forecasting accuracy.

Additionally, the modeling was conducted using the fable package in the R programming language, employing an automatic time series procedure for ETS, ARIMA, and ATA models. In this context, classical decomposition was selected as the seasonal approach for ATA_seasonal, while an automatic time series forecasting procedure was utilized for ATA_full.

Table 1. Accuracy Performance of Utilized Forecasting Methods. *ME (Mean Error), RMSE (Root Mean Squared Error),MAE (Mean Absolute Error), MPE (Mean Percentage Error),MAPE (Mean Absolute Percentage Error),MASE (Mean Absolute Scaled).*

Model	Type	ME	RMSE	MAE	MPE	MAPE	MASE
arima	Test	23	116	92.9	-32.8	75.7	1.13
ata_full	Test	-40.6	**110**	**90.1**	-83.5	97.1	**1.09**
ata_seasonal	Test	-111	169	135	-95	101	1.64
ata_simple	Test	-186	213	195	-212	214	2.37
ets	Test	93.9	142	97.8	41.8	**45.3**	1.19
mixed	Test	-8.82	**106**	**86.9**	-58.1	83.9	**1.06**

The assessment of forecasting methods on the test dataset highlights notable variations in accuracy performances across different measures. Despite these differences, the performance of the ATA_full model stands out, particularly excelling when compared to other models. The combination of ARIMA and forecasting yields noteworthy results, drawing attention to the effectiveness of this tandem approach. The ARIMA model demonstrates mixed results, exhibiting a substantial mean error (ME) but relatively low root mean squared error (RMSE) and mean absolute error (MAE). The ATA_full model, despite a significant negative ME, achieves a balanced performance with comparable RMSE and MAE values. On the other hand,

the ATA_seasonal and ATA_simple models show elevated errors across all measures, indicating challenges in capturing the underlying patterns in the test data. The ETS model stands out with a notably high ME but competitive RMSE and MAE values, suggesting its effectiveness in predicting the direction of the data, albeit with larger errors. Lastly, the Mixed model displays a balanced performance across all measures, reflecting its versatility in capturing diverse patterns within the test dataset.

This assessment underscores the importance of considering multiple accuracy metrics to comprehensively evaluate forecasting methods, providing researchers with nuanced insights into their respective strengths and weaknesses.

Upon examining Figure 2, it is observed that the combination of univariate models enhances forecast performance, as evidenced by the original observations, forecast values, and confidence intervals present in the chart.

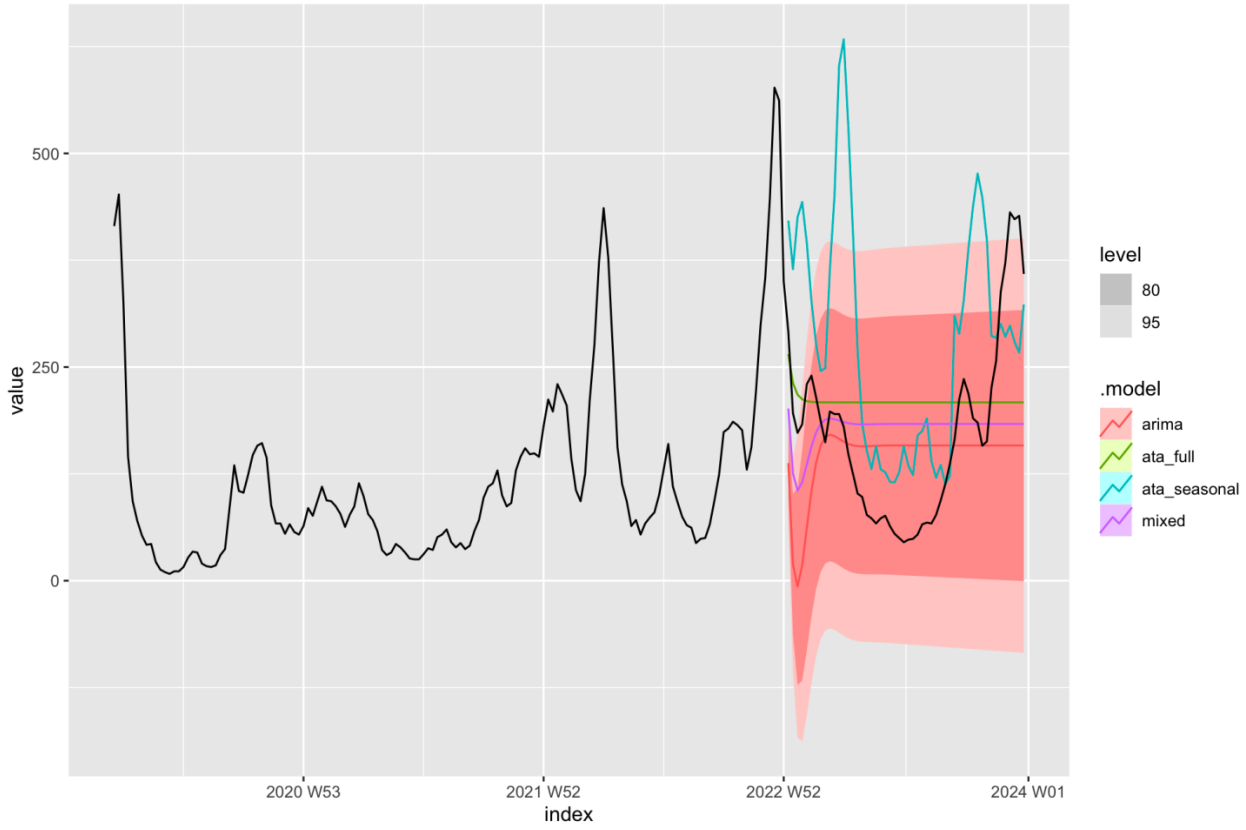

Figure 2. Forecasting Performance of Univariate Methods for Test Data (Rate per 100 000 inhabitants).

Examining Figure 3 and delving into the insights derived from Table 2, we come across a notable finding. The Ata_full model, showcasing the best solo performance, has seamlessly combined its forecasting strength with the second-best, the ARIMA model. This combination,

aptly named "Mixed," cleverly blends the simple averages of forecast values from these two standout performers. The resulting combined model, supported and reinforced by existing scholarly works, stands as a testament to its improved predictive precision.

DISCUSSION

Time series forecasting of the incidence rates of ARI and COVID-19 in France faces several challenges. One challenge is the heterogeneity between regions, which highlights the need for local-level forecasts [19]. Another challenge is the non-seasonal and non-stationary nature of the pandemic, requiring specialized forecasting methods [20]. Additionally, incomplete and varying data from different hospitals can lead to misleading estimates of the real spread of the virus [21,22]. The availability of a large amount of COVID-19 related data serves as a motivation to develop mathematical models for predicting the course of the epidemic [23]. Furthermore, the complexity of the epidemic and the need to predict the peak and end of the epidemic make forecasting challenging. The application of popular univariate forecasting methods, widely recognized in the literature for their high accuracy in forecasting, and obtaining method combinations can enhance the predictions of incidence rates.

The evaluation of each forecasting model was conducted meticulously, considering key metrics such as RMSE, MAE, MAPE, and MASE. The ARIMA model exhibited commendable predictive accuracy, as indicated by its low RMSE of 116. However, a negative MPE of -32.8 suggested a tendency to consistently underestimate values. The ATA_full model emerged as a standout performer, showcasing competitive metrics with a RMSE of 110 and an impressive MAPE of 97.1. Despite its significant negative MPE of -83.5, emphasizing an underestimation trend, the model demonstrated notable effectiveness in capturing the underlying patterns. The ATA_seasonal model, while effective with a RMSE of 169 and a MAPE of 101, displayed a slightly higher MASE of 1.64, indicating room for improvement in forecasting accuracy. Notably, the ATA_simple model encountered challenges, reflected in the highest RMSE, MAPE, and MASE values, coupled with a substantial negative MPE of -212, suggesting significant difficulties in providing accurate forecasts. The ETS model exhibited reliable and scaled forecasts, characterized by a low RMSE, a favorable MAPE of 45.3, and a MASE of 1.19. Finally, the mixed model displayed a balanced performance, featuring a modest underestimation trend (-58.1), a competitive MAPE of 83.9, and a commendable MASE of 1.06. This nuanced analysis underscores the ATA_full model's noteworthy performance,

particularly in the context of the MASE metric, emphasizing its effectiveness in capturing the intricate dynamics of the data.

With a keen eye on the upcoming 2024 horizon, this combined model presents its forecasted values for the first 13 weeks, thoughtfully laid out in the Mixed column of Table 2. The implications of this predictive ability suggest an expected decrease in incidence rates,

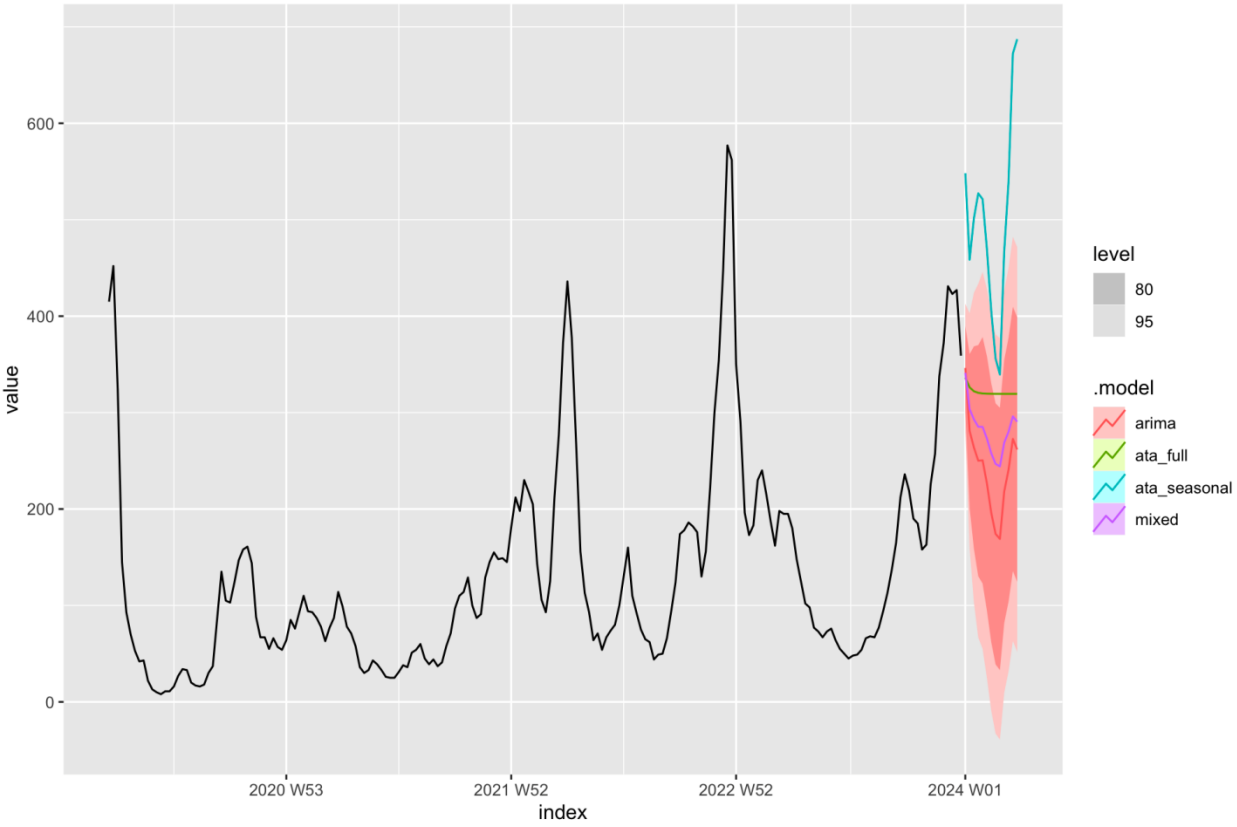

Table 2. Forecast of Covid-19 Incidence Rates of Acute Respiratory Infections (ARI) for the 13-Week Horizon in 2024 Using Different Time Series Methods (Rate per 100 000 inhabitants).

Week	ETS	ARIMA	ATA_seasonal	ATA_full	Mixed
2024 W01	340	346	548	336	**341**
2024 W02	324	281	459	326	**304**
2024 W03	312	264	502	322	**293**
2024 W04	302	250	527	320	**285**
2024 W05	294	251	521	320	**285**
2024 W06	287	227	469	320	**273**
2024 W07	282	196	406	319	**258**
2024 W08	278	174	356	319	**247**
2024 W09	275	169	339	319	**244**

2024 W10	272	218	467	319	**269**
2024 W11	270	241	539	319	**280**
2024 W12	268	273	672	319	**296**
2024 W13	267	262	687	319	**291**

In the first 13 weeks of 2024, the forecasted Covid-19 incidence rates of Acute Respiratory Infections (ARI) using different time series methods exhibit distinct values. For instance, in the ETS method for the 13th week, the forecasted rate is 267 per 100,000 inhabitants, while ARIMA forecasts it at 262. ATA_seasonal suggests a higher value of 687, ATA_full forecasts 319, and the Mixed method indicates 291. These forecasts illustrate the diverse outcomes generated by each forecasting technique. The variations in forecasts underscore the importance of selecting an appropriate forecasting model for accurate and reliable insights into the trajectory of ARI incidence rates during the 13-week period in 2024

CONCLUSION

In conclusion, this study contributes to the ongoing efforts in understanding and managing the trajectory of the COVID-19 pandemic by evaluating the predictive capabilities of the ATA univariate forecasting method, ARIMA, and ETS models. Through a meticulous analysis of Acute Respiratory Infections (ARI) incidence rates in France, spanning from 2020 to 2023, these models were applied to offer valuable insights into forecasting future incidence rates.

The comparative assessment of these forecasting models revealed diverse performances across various accuracy measures. The ATA_full model emerged as a standout performer, showcasing superior accuracy, particularly when compared to other models. The combination of ARIMA and ATA forecasting, referred to as the "Mixed" model, demonstrated noteworthy results, emphasizing the effectiveness of this combined approach.

Examining the forecasted values for the first 13 weeks of 2024, presented in Table 2, the combined model predicts a decrease in incidence rates. These findings underscore the importance of considering multiple accuracy metrics for a comprehensive evaluation of forecasting methods.

As we navigate the complex landscape of infectious disease prediction, this study emphasizes the significance of adopting versatile and robust forecasting models for strategic planning and effective management of public health crises. The insights gained from this research contribute to the evolving understanding of the dynamics surrounding COVID-19 incidence rates,

providing a foundation for informed decision-making in the field of infectious disease forecasting.

Limitation

In this study, it should be noted that there is no inherent limitation to forecast due to the use of a pre-organized dataset.

Acknowledgment

The dataset used in this study belongs to a health data platform named “Sentiweb”, which serves for monitoring and analyzing various diseases in the region in Southern France. This platform facilitates the tracking of various diseases affecting public health and visualizes this data “Sentiweb” aims to provide access to health statistics for healthcare professionals, researchers, and the general public, contributing to understanding the regional health situation. I would like to express my gratitude to this organization for enabling the opportunity to contribute to my research goal.

Conflict of interest

The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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