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COMPARISON OF EXERCISE CAPACITY, PHYSICAL ACTIVITY LEVEL AND QUALITY OF LIFE IN CHILDREN WITH PRIMARY IMMUNODEFICIENCY WITH HEALTHY CHILDREN

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MASTER OF SCIENCE

DEPARTMENT OF PHYSIOTHERAPY AND REHABILITATION

GAZİ UNIVERSITY

GRADUATE SCHOOL OF HEALTH SCIENCES

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(M.Sc. Thesis)

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ABSTRACT

Primary immune deficiencies (PIDs) include a variety of diseases affecting immune system development, differentiation, and function. Pulmonary and extrapulmonary manifestations are not well investigated and which may possibly contribute to morbidity and mortality in patients with PIDs. This study aimed to compare maximal exercise capacity (CPET), functional exercise capacity (6-MWT), pulmonary function (spirometry), physical activity (Metabolic holter), quality of life (PedsQL), respiratory muscle strength (MIP, MEP), endurance (threshold loading test), peripheral muscle strength (dynamometer), muscle oxygenation (Moxy® monitor), and dyspnea in patients with PID and healthy children. Fourteen patients with PID and 15 healthy children were compared. No significant differences were prevalent between groups in FVC, FEV_1, PEF, $FEF_{25-75\%}$, MIP, MEP, respiratory muscle endurance ($p>0.05$). Patients exhibited significantly lower shoulder abductor strength (%), knee extensor strength (%), 6-MWT distance, $peakVO_{2kg}$, $EqCO_2$ active energy expenditure, number of steps, and average MET values ($p<0.05$). During 6MWT, patients had lower SmO_{2max} (%), ΔSmO_2 (%), $SmO_{2avg-max}$ (%), and ΔSmO_{2avg} (%), and during CPET, patients had lower SmO_{2rest} (%), SmO_{2max} (%), $SmO_{2avg-max}$ (%), and $SmO_{2recovery-avg}$ (%) ($p<0.05$). Patients reported higher dyspnea and lower psychosocial health, physical health, and total PedsQL scores compared to healthy ($p<0.05$). In conclusion patients with PID have impaired functional and maximal exercise capacity, decresed physical activity levels and quality of life, upper and lower extremity muscle weakness, and reduced muscle oxygenation during 6-MWT, CPET with normal pulmonary function and respiratory muscle strength. Routinelly evaluation of pulmonary and extrapulmonary manifestations are warranted and effects pulmonary rehabilitation need to be investigated in patients.

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PRİMER İMMÜN YETMEZLİĞİ OLAN ÇOCUKLARIN EGZERSİZ KAPASİTESİ, FİZİKSEL AKTİVİTE SEVİYESİ VE YAŞAM KALİTESİNİN SAĞLIKLILARLA KARŞILAŞTIRILMASI

(Yüksek Lisans Tezi)

Riad BEJTA

GAZİ ÜNİVERSİTESİ
SAĞLIK BİLİMLERİ ENSTİTÜSÜ

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ÖZET

Amaç

Primer immün yetmezlikler (PİY) immün sistemde yer alan çeşitli hücre ve yapı taşlarının gelişim, farklılaşma ve/veya fonksiyonunu etkileyen bozukluklar sonucunda ortaya çıkan heterojen bir hastalık grubudur. PİY'ler klinik olarak enfeksiyonlar, otoimmünite, otoinflamatuvar hastalıklar, alerji, kemik iliği yetmezliği ve/veya maligniteye karşı artmış duyarlılık ile kendini gösterir. Bireysel olarak nadir olmakla birlikte, PİY bireylerin toplam sayısı önemli bir sağlık yükü oluşturur. PİY prevalansı ve dağılımı toplumlar arasında değişiklik göstermektedir ve prevalansının 1/1,000-1/5,000 olduğu tahmin edilmektedir. PİY'lerin Türkiye'deki prevalansı bu konuda geniş çalışmalar ve ulusal kayıt sistemi olmadığı için net olarak bilinmemektedir. Ancak Türkiye'de iki merkezi kapsayan bir çalışmada PİY prevalansı 30,5/100,000 olarak bildirilmiştir. Günümüzde yaklaşık 500 çeşit PİY hastalığı tanımlanmıştır. En sık görülen PİY hastalığı selektif IgA eksikliği, en sık görülen semptomatik PİY hastalığı ise yaygın değişken immün yetmezliktir.

PİY hastalıklarının semptomları ve komplikasyonları arasında pulmoner komplikasyonlar çok yaygındır ve hastalığın morbidite ve mortalitesini önemli ölçüde artırmaktadır. Tekrarlayan solunum yolu enfeksiyonları genellikle bazı PİY'lerde ilk uyarı işaretini oluşturur ve PİY'li erişkinlerde mortalite nedenidir. Yılda 2 iki veya daha fazla pnömoni varlığı, PİY'nin 10 uyarı işaretinden biridir.

Solunum sistemi hastalıklarını başlıca akut ve kronik enfeksiyonlar oluşturur. Enfeksiyöz olmayan solunum sistemi hastalıkları ve komplikasyonlarını ise astım, bronşiektazi, bronşiolitis obliterans, interstisyel akciğer hastalığı, granülomatöz akciğer hastalığı ve

maligniteler oluşturur. Bu hastalıklar PİY hastalarının yaşam kalitesini önemli ölçüde etkiler, çalışma yeteneklerini, fiziksel ve sosyal aktivitelerini sınırlar. PİY hastalarında sağlıkla ilişkili yaşam kalitesi, enfeksiyonların teşhis ve tedavisindeki gecikmelerden de önemli ölçüde olumsuz etkilenir. Enfeksiyonlardan sağ kalım arttıkça enfeksiyöz olmayan pulmoner komplikasyonlar PİY hastalarında daha sık görülmektedir. Özellikle antikor eksikliği ile seyreden PİY'li hastalarda %20-40 oranında kalıcı akciğer hasarı görülmektedir.

PİY hastalarda fiziksel aktivite düzeyleri de etkilenir, ancak bu konuda sadece anket çalışmaları vardır. Dolaysıyla bu hastalarda solunum kas kuvveti ek olarak solunum kas enduransı, fonksiyonel egzersiz kapasitesi ve periferik kas gücü etkilenmesi beklemektedir. Yine fonksiyonel egzersiz kapasitesi, solunum kas kuvveti ve dayanıklılığı, periferik kas kuvvetini araştıran hiç araştırma yoktur.

Bu çalışmanın amacı, primer immün yetmezlik hastalarında maksimal egzersiz kapasitesi fonksiyonel egzersiz kapasitesi, solunum fonksiyonları, fiziksel aktivite seviyesi, yaşam kalitesi, solunum kas kuvveti ve enduransı, periferik kas kuvveti ve dispnenin sağlıklı bireylerle karşılaştırılmasıdır. Çalışmamızın sonucunda elde edilecek bilgiler klinik uygulamalar ve farklı yöntemlerin kullanıldığı ileri çalışmalar için yön gösterici olacaktır.

Bu çalışmanın birincil sonuç ölçütleri maksimal egzersiz kapasitesi, fonskiyonel egzersiz kapasitesi, fiziksel aktivie seviyesidir. İkincil sonuç ölçütleri kas oksijenizasyonu, solunum fonksiyonları, solunum kas kuvveti ve endruansı, periferik kas kuvveti, yaşam kalitesi ve dispnedir.

Çalışmanın Hipotezleri

Birincil amaç için hipotezler:

H0: Primer immun yetmezlik hastaları ile sağlıklı çocukların maksimal egzersiz kapasitesi, fonksiyonel egzersiz kapasitesi ve fiziksel aktivite seviyeleri arasında fark yoktur.

H1: Primer immun yetmezlik hastaları ile sağlıklı çocukların maksimal egzersiz kapasitesi, fonksiyonel egzersiz kapasitesi ve fiziksel aktivite düzeyleri arasında fark vardır.

İkincil amaç için hipotezler:

H0: Primer immun yetmezlik hastaları ile sağlıklı çocukların solunum fonksiyonları, solunum kas kuvveti, solunum kas endüransı, periferik kas kuvveti, kas oksijenizasyonu, yaşam kalitesi, ve dispne arasında fark yoktur.

H1: Primer immun yetmezlik hastaları ile sağlıklı çocukların solunum fonksiyonları, solunum kas kuvveti, solunum kas endüransı, periferik kas kuvveti, kas oksijenizasyonu, yaşam kalitesi, ve dispne arasında fark yoktur.

Gereç ve yöntem

Mayıs/2023 ile Mayıs/2024 tarihleri arasında Dr. Sami Ulus Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi Çocuk İmmünoloji ve Alerji Hastalıkları Bölümünde primer immün yetmezlik tanısı konulan hastalar Gazi Üniversitesi, Sağlık Bilimleri Fakültesi, Kardiyopulmoner Fizyoterapi ve Rehabilitasyon Ünitesinde kardiyopulmoner rehabilitasyon için yönlendirilmiştir. Çalışmaya 14 hasta ve 15 yaş ve cinsiyet eşleştirilmiş sağlıklı çocuk dahil edildi. Sağlıklı çocukları çalışmaya davet etmek için üniversite giriş kapılarına araştırmayı anlatan ilanlar asıldı. Verilen telefon numaralarıyla iletişime geçerek gönüllü olan çocuklar katılmaya davet edilmiştir.

<u>Hastalar için içleme öçütleri:</u>

- Avrupa İmmün Yetmezlikler Derneği (ESID) tanısal klinik kriterlerine göre primer immün yetmezlik tanısı olan hastalar.

- Her iki cinsiyetten, 6-18 yaş hastalar

- Klinik durumu stabil olan hastalar

<u>Hastalar için dışlama ölçütleri:</u>

- Fiziksel aktiviteyi engelleyen rahatsızlıkları olanlar (örn. ortopedik, nörolojik veya psikolojik kısıtlamalar).

- Değerlendirme sırasında veya son bir ay içinde akut enfeksiyon geçiren bireyler

<u>Sağlıklı kontroller için içleme ölçütleri:</u>

- 6-18 yaş arası bireyler

- Çalışmaya gönüllü olarak katılmak isteyenler

Sağlıklı kontroller için dışlama ölçütleri:

- Teşhis edilmiş herhangi bir hastalığı olan bireyler

- Değerlendirme sırasında veya bir ay içinde akut enfeksiyonu olanlar.

Çalışma enine kesitsel olarak planlanmıştır. Primer immün yetmezlik tanılı hastaların medikal takipleri immünoloji hekimi tarafından yapıldı. Çalışma için tıbbi muayene, tanı, radyolojik takip, laboratuvar testler, genetik testler ve tedavi bilgileri hastaların dosyasından kaydedildi. Değerlendirmeler Gazi Üniversitesi Sağlık Bilimleri Fakültesi Kardiyopulmoner Fizyoterapi ve Rehabilitasyon Ünitesinde iki günde gerçekleştirilmiştir. İlk gün, hastalar ve sağlıklı kontrollerin solunum fonksiyonları, solunum ve kas kuvveti, fonksiyonel egzersiz kapasitesi ve solunum kas enduransı değerlendirildi. İkinci gün maksimal egzersiz kapasitesi ve yaşam kalitesi değerlendirilmiştir. Maksimal egzersiz kapasitesi kardiyopulmoner egzersiz testi (KPET), fonksiyonel egzersiz kapasitesi 6-dakika yürüme test (6-DYT), fiziksel aktivite seviyesi metabolik holter, solunum fonksiyonları spirometre, solunum kas kuvveti ağız basınç ölçüm cihazı, solunum kas enduransı artan eşik yükü solunum kas enduransı testi, periferik kas kuvveti taşınabilir dijital el dinamometresi, kas oksijenizasyonu Moxy® mönitor, yaşam kalitesi Çocuklar İçin Yaşam Kalitesi Ölçeği (ÇİYKÖ), dispne Modifiye Borg ölçeği (M. Borg) Türkçe uyarlamaları kullanılarak değerlendirilmiştir.

Bireylerin Değerlendirilmesi

Çalışma sırasında hem hastaların hem de sağlıklı bireylerin demografik özellikleri kaydedilmiştir. Boy metre (m) ve ağırlık kilogram (kg) cinsinden ölçülmüştür. Vücut kitle indeksi (VKİ), ağırlığın (kg) boyun karesine (m^2) bölünmesiyle hesaplandı ve elde edilen VKİ değerleri kaydedildi. Hem bireyden hem de ailesinden semptom başlangıç yaşı ve tanı, kişisel tıbbi öykü, eşlik eden hastalıklar, mevcut ilaçlar, sigara maruziyeti, kilo dalgalanmaları ve yeme güçlükleri, ailede akraba evliliği öyküsü, eğitim durumu, egzersiz alışkanlıkları, fizik muayene, laboratuvar çalışmaları, radyolojik bulgular, histopatolojik bulgular ve genetik testlerin kaydedilmesini içeren ayrıntılı bir tıbbi öykü alınmıştır.

Semptomların Değerlendirilmesi

Hastalardan detaylı bir akciğer sağlığı öyküsü alınmıştır. Bu kapsamda öksürük, balgam, dispne, hemoptizi ve ortopne ile ilgili sorular sorulmuştur. Hem dinlenme hem de efor dispnesinin yanı sıra efor dispnesini tetikleyen aktivitelere odaklanılarak dispnenin şiddeti ve sorulmuştur.

Solunum Fonksiyon Testi

Solunum fonksiyon test ölçümleri Amerikan Toraks Derneği (ATS) ve Avrupa Solunum Derneği (ERS) ölçütlerine göre taşınabilir spirometre (Cosmed, Class II/ Internally Powered Equipment, Italy) cihazı ile değerlendirildi. Solunum fonksiyon testinde zorlu vital kapasite (FVC), zorlu ekspirasyonun birinci saniyesinde çıkarılan hava hacmi (FEV_1), zorlu ekspirasyonun birinci saniyesinde çıkarılan hava hacminin zorlu vital kapasiteye oranı (FEV_1/FVC), tepe ekspiratuar akım hızı (PEF) ve zorlu ekspiratuar hacmin %25-75'indeki akım hızı ($FEF_{\%25-75}$) ölçüldü.

Solunum Kas Kuvveti

Solunum kas kuvveti taşınabilir, elektronik ağız basınç ölçüm cihazı (Micro Medical MicroRM, İngiltere) kullanarak değerlendirildi. Maksimum inspiratuar basınç (MİP) ve maksimum ekspiratuar basınç (MEP) ölçüldü. Ölçümler en az 7 kere tekrarlandı ve ölçüm basınçları santimetre su (cmH_2O) cinsinden kaydedildi. Domenech-Clar ve arkadaşlarının referans eşitleri kullanılarak MIP ve MEP ölçümleri değerlendirildi.

Solunum Kas Enduransı

Solunum kas enduransı değerlendirmesi inspiratuar kas eğitim cihazı (Power Breathe®, HaB International Ltd. Southam, İngiltere) ve artan eşik yükleme solunum kas endurans testi ile değerlendirildi. Cihaz ağızdan çıkarılmadan basınç artırıldı ve toplam test süresi ile en az bir dakika boyunca sürdürebildiği ulaşılan maksimum basınç değerinin çarpımı ile solunum kas enduransı değeri elde edildi ve cmH_2O/sn cinsinden kaydedildi. Test esnasında teknik olarak kabul edilebilir en az üç manevradan en iyisi analiz için kaydedildi.

Periferik Kas Kuvveti

Omuz abdüktörler ve diz ekstansörlerin izometrik kas kuvveti taşınabilir el dinamometresi (JTECH Power Track Commander, Baltimore, ABD) ile değerlendirildi. Hastaların omuz abdüktör kuvveti kol 90º abdüksiyonda ve diz ekstansör kuvveti diz 90º ekstansiyonda

desteksiz dik oturma pozisyonunda değerlendirildi. Testler sağ ve sol taraflarda üç kere tekrarlandı. Ölçümler Newton (N) cinsinden kaydedildi ve analiz için ölçümlerden en yüksek değer alındı. Beklenen kas kuvveti değeri Beenakker ve arkadaşlarının referans eşitliği kullanılarak hesaplandı.

Maksimal Egzersiz Kapasitesi: Kardiyopulmoner Egzersiz Testi

Maksimal egzersiz kapasitesini değerlendirmek için Kardiyopulmoner Egzersiz Testi (KPET) kullanıldı. Kardiyopulmoner egzersiz testi, pulmoner, kardiyovasküler, metabolik ve hematolojik sistemlerin entegre yanıtının genel bir değerlendirmesini sağladı. Ölçümler metabolic cart (Quark CPET, Cosmed, Italy) kullanılarak koşu bandında (Trackmaster, 3017 Full Vision, Newton, Ks ABD) yapıldı. Test boyunca kalp hızı (HR), oksijen satürasyonu (SpO_2), arteriyel kan basıncı ve 12 derivasyonlu EKG (hız, ritim ve S-T segment morfolojisi değerlendirmesi için) izlendi. Her test öncesinde cihazın kalibrasyonu yapıldı. Bu test üç aşamadan oluştu: istirahat, yükleme ve dinlenme. İlk üç dakikada bireylerin istirahat verileri kaydedildi, sonrasında her üç dakikada bir iş yükü artırıldı. İş yükü artışları 10–50-watt olarak ayarlandı. Birey maksimum kalp hızına ulaşana kadar teste devam edildi, herhangi bir semptom (nefes darlığı, göğüs ağrısı, yorgunluk, ST segment elevasyonu) meydana geldiğinde ise test durduruldu.

Fonksiyonel Egzersiz Kapasitesi

Fonksiyonel egzersiz kapasitesi Altı Dakika Yürüme Testi (6-DYT) ile değerlendirildi. Test, ATS ölçütlerine uygun olarak değerlendirildi. Altı-DYT 30 metre düz bir koridorda yapıldı, testin başlangıç ve bitiş noktaları konilerle işaretlendi. Test öncesi, sonrası ve 1. dakika toparlanmada hastaların kalp hızı, kan basıncı, oksijen satürasyonu, solunum frekansı, dispne, yorgunluk ve bacak yorgunluğu algısı kaydedildi. Bu ölçümlerde kalp hızı kalp hızı monitörü (Polar FT I00, Çin), kan basıncı sfigmomanometre, oksijen satürasyonu taşınabilir pulse oksimetre (Model 9590 Oximeter Nonin ® Medical, Inc, Plymouth, MN, ABD), dispne, yorgunluk ve bacak yorgunluğu algılanması Modifiye Borg Ölçeği ile, solunum frekansı bir dakikada aldığı soluklar sayılarak değerlendirildi. Analiz için iki testin arasında en uzun yürüme mesafesi seçildi. Li ve arkadaşlarının referans eşitliği kullanılarak, hastaların beklenen 6-DYT yürüme mesafesi hesaplandı.

Fiziksel Aktivite Seviyesi

Fiziksel aktivitenin değerlendirilmesi metabolik holter (Sensewear, BodyMedia, Inc Pittsburgh, ABD) cihazı kullanılarak değerlendirildi. Çok sensörlü metabolik holter cihazı ile elde edilen toplam enerji harcaması (joule/gün), 3 metabolik eşdeğerin (MET) üstündeki aktif enerji harcaması (joule/gün), ortalama MET değeri (MET/gün), adım sayısı (adım/gün), fiziksel aktivite süresi (dakika/gün), yatarak geçen süre (dakika/gün), uyku süresi (dakika/gün) ve vücutta kaldığı toplam süre (dakika/gün) verileri kaydedildi. "BodyMedia® SenseWear® 7.0 Software" analiz programı ile yaş, cinsiyet, boy ve kilo bilgileri kullanılarak kaydedildi. Hastaların cihazdan kaydedilen adım sayısı verilerine göre fiziksel aktivite düzeyleri belirlendi.

Kas Oksijenizasyonu

Kas oksijenizasyonu "Moxy®" monitör (Moxy, Fortiori Design LLC, Minnesota, ABD) ile değerlendirildi. Altı-DYT ve KPET esnasında Quadricps kası motor noktasına cihaz yerleştirildi. SmO_2 ($SmO_{2istirahat}$) ve total hemoglobin ($THb_{istirahat}$), 6-DYT sırasındaki SmO_2, ortalama SmO_2 (SmO_{2ort}) ve total hemoglobinin minimum ve maksimum değerleri (SmO_{2min}, SmO_{2max}, $\Delta SmO2$, $SmO_{2ort\text{-}min}$, $SmO_{2ort\text{-}max}$, ΔSmO_{2ort}, THb_{min}, THb_{max}, ΔTHb) değerleri ve toparlanmanın birinci dakikasında SmO_2, SmO_{2ort} ve THb (SmO_{2top}, $SmO_{2top\text{-}ort}$, THb_{top}) değerleri kaydedildi. Kas oksijen satürasyonu değerleri yüzde (%), THb g/dl cinsinden ifade edildi. Cihazın geçerlik ve güvenilirliği kanıtlanmış ve test-tekrar test güvenirliği yapılmıştı.

Yaşam Kalitesi

Yaşam kalitesi ölçümleri, Varni ve diğerleri tarafından 1999 yılında geliştirilen Çocuklar için Yaşam Kalitesi Ölçeği (ÇİYKÖ) kullanılarak gerçekleştirildi. Bu ölçek, toplam 23 madde ve 4 alt ölçekten oluşmaktadır: Fiziksel işlevselliği ölçen 8 madde, duygusal işlevselliği ölçen 5 madde, sosyal işlevselliği ölçen 5 madde ve okuldaki işlevselliği değerlendiren 5 madde içermektedir. Ölçek, dört farklı yaş grubu için uygundur: 2-4 yaş, 5-7 yaş, 8-12 yaş ve 13-18 yaş. Hem çocuklar hem de ebeveynler için farklı formları bulunmaktadır. Çocuklar için 5-7 yaş, 8-12 yaş ve 13-18 yaş için ayrı ölçekler mevcuttur. Ebeveynler için ise, 2-4 yaş, 5-7 yaş, 8-12 yaş ve 13-18 yaş için ayrı formları bulunmaktadır. Maddeler 0 ile 100 arasında puanlanmaktadır. Sorunun yanıtı hiçbir zaman olarak işaretlenmişse 0=100, nadiren olarak işaretlenmişse 1=75, bazen olarak işaretlenmişse 2=50, sıklıkla olarak işaretlenmişse 3=25, hemen her zaman olarak işaretlenmişse 4=0 puan

almaktadır. Puanlar toplanıp doldurulan madde sayısına bölünerek toplam puan elde edilir. ÇİYKÖ toplam puanı ne kadar yüksekse, sağlıkla ilgili yaşam kalitesi o kadar iyi algılanmaktadır.

İstatistiksel Analiz

İstatistiksel analiz Windows tabanlı bir program olan SPSS 27 kullanılarak gerçekleştirilmiştir. Bu çalışmada %80 güç ve %5 tip 1 hata ile elde edilen mevcut çalışma verilerine dayanarak zirve VO_{2kg} değerlerine göre en az 11 PİY hastası ve 11 sağlıklı çocuk çalışmaya dahil edilmesine hesaplandı. Değişkenlerin normalliği hem görsel olarak (histogramlar ve olasılık grafikleri kullanılarak) hem de analitik olarak (Kolmogorov-Smirnov ve Shapiro-Wilk testleri aracılığıyla) değerlendirilmiştir. Tanımlayıcı analizler, normal dağılımlı değişkenler için %95 güven aralığı (%95 CI) ve standart sapma ile ortalama farkı, sayılabilir değişkenler için yüzdeleri (%) ve normal dağılımlı olmayan değişkenler için minimum ve maksimum değerlerle birlikte medyanı sunmuştur. Normal dağılım gösteren değişkenler için karşılaştırma amacıyla bağımsız örneklem t-testi (Student's t-test) kullanılırken, normal dağılım göstermeyen veriler için Mann-Whitney U testi kullanılmıştır. Kategorik veriler Ki-kare testi kullanılarak analiz edilmiştir. İstatistiksel analiz için anlamlılık düzeyi $p \leq 0.05$ olarak belirlenmiştir. Sonuçlar, zirveVO_{2kg} değerleri kullanılarak post-hoc güç analizi yapılarak yorumlanmıştır.

Bulgular

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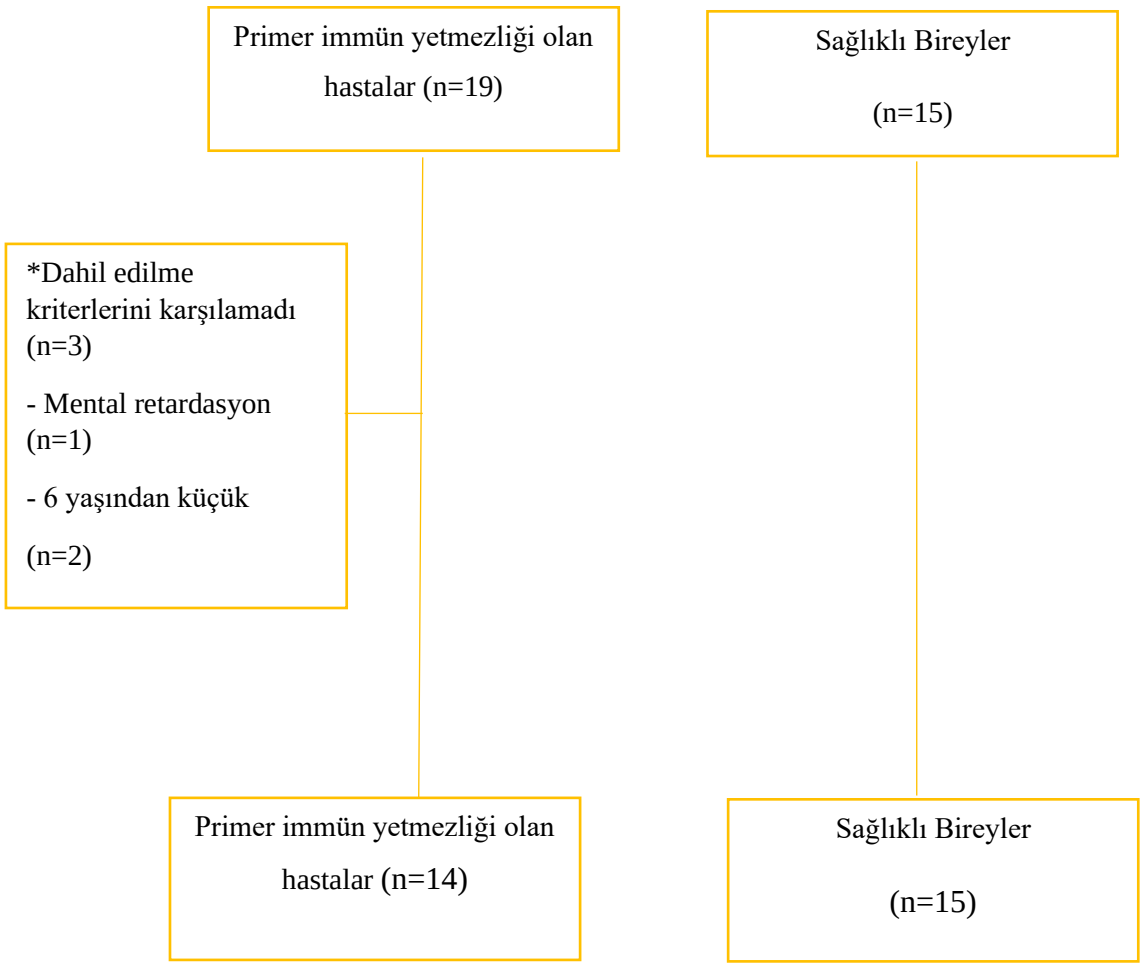

Şekil 4.1. Primer immün yetmezliği olan hastaların ve sağlıklı bireylerin "STROBE" akış şeması.

Bulgular:

- Primer immün yetmezliği olan hastaların ve sağlıklı çocukların yaş, boy, vücut ağırlığı, vücut kitle indeksi ve Z-skorları istatistiksel olarak benzerdi ($p>0,05$).
- Primer immün yetmezliği olan hastaların ve sağlıklı çocukların cinsiyet dağılımları istatistiksel olarak benzerdi ($p>0,05$).
- Primer immün yetmezliği olan hastaların ve sağlıklı çocukların boy Z skoru dağılımları istatistiksel olarak benzerdi ($p>0,05$).
- Primer immün yetmezliği olan hastaların ve sağlıklı çocukların vücut ağırlığı Z skoru dağılımları istatistiksel olarak benzerdi ($p>0,05$).
- Primer immün yetmezliği olan hastaların ve sağlıklı çocukların vücut kitle indeksi Z skoru dağılımları istatistiksel olarak benzerdi ($p>0,05$).

- Primer immün yetmezliği olan hastalar ile sağlıklı çocuklar arasındaki eğitim düzeyi benzerdi (p>0,05).
- Primer immün yetmezliği olan hastalar ile sağlıklı çocuklar arasında akraba evliliği açısından anlamlı bir fark vardı. Hastaların yüzde ellisinin ailesinde akraba evliliği öyküsü vardı (p<0,05).
- Primer immün yetmezlik hastalarının %85,7'si intravenöz immünglobulin G tedavisi alıyordu.
- Hastalardan %42,9 profilaktik antibyotik kullanıyordu.
- Primer immün yetmezliği olan hastalarda genetik mutasyonları: BTK (n=3, %21,4), CTLA4 (n=2, %14,4), MAGT1 (n=1, %7,1), TAPBP (n=1, %7,1), IGLL1 (n=1, %7,1), RFX5 (n=1, %7,1), TNFRSF6 (n=1, %7,1), belirsiz (n=4, %28,7) idi.
- Uluslararası İmmünoloji Dernekleri Birliği'nin Doğuştan Bağışıklık Hataları sınıflandırmasına göre primer immün yetmezliği olan hastaların dağılımı: Kombine immün yetmezlikler (n=2, %14,3), Ağırlıklı olarak antikor eksiklikleri (n=8, %57,2), Bağışıklık düzensizliği hastalığı (n=3, %21,4), Doğuştan gelen bağışıklık hatasının fenokopileri (n=1, %7,1) idi.
- Primer immün yetmezliği olan hastalarda bir yıl içinde alevlenme durumu ve hastane ziyaret sayısı: alevlenme sayısı (0 (0-0)), hastane ziyaret sayısı (12 (12-12)) idi.
- Primer immün yetmezliği olan hastalarla sağlıklı çocuklar arasında egzersiz alışkanlıkları açısından istatistiksel bir fark yoktu.
- Primer immün yetmezliği olan çocukların efor dispnesi algıları sağlıklı çocuklara göre istatistiksel anlamlı daha fazlaydı (p<0,05).
- Hastaların FEV1/FVC'si sağlıklı çocuklara göre istatistiksel anlamlı olarak azdı. (p<0,05). Grupların FVC (L), FVC (%), FEV_1 (L), FEV_1 (%), PEF (L), PEF (%), $FEF_{25-75\%}$ (L), $FEF_{25-75\%}$ (%) parametreleri istatistiksel olarak benzerdi (p>0,05). Hastaların dördünde (%28,57) obstrüktif, ikisinde (%14,29) miks ve birinde (%7,17) restriktif tipte solunum fonksiyon bozukluğu vardı.
- Hastaların MEP (%) değeri sağlıklı çocuklara göre istatistiksel olarak anlamlı olarak azalmıştı (p<0,05). Gruplarda MIP, MIP (%), MEP değerleri istatistiksel olarak benzerdi (p>0,05). Altı (%42,86) hastanın MIP'i ve üç (%21,43) hastanın MEP'i beklenenin %80'inden azdı.

- Solunum kas enduransı (cmH_2O), (%), SpO_2 (istirahat) (%), dispne (istirahat), ΔSpO_2 (%) ve ΔDispne değerleri gruplarda istatistiksel olarak benzerdi ($p>0,05$). Dokuz (%64,28) hastanın solunum kas enduransı beklenenin %80'inden azdı.
- Primer immün yetmezliği olan hastaların sağ diz ekstansörleri (%) ve sağ omuz abduktörleri (%) kas kuvvetleri sağlıklı çocuklara göre istatistiksel olarak anlamlı azalmıştı ($p<0.05$). Sağ diz ekstansör kas kuvveti (N) ve sağ omuz abduktor kas kuvveti (N) gruplarda istatistiksel olarak benzerdi ($p>0,05$). Dokuz hastanın sağ diz ekstansör kas kuvveti (%64,28), sekiz hastanın sol diz ekstansör kas kuvveti ($p>0,05$) %57,14), sekiz hastanın (%57,14) sağ omuz abdüktör kas kuvveti ve 10 hastanın (%71,42) sol omuz abdüktör kas kuvveti beklenenin %80'inden azdı.
- Hastaların 6-DYT mesafesi sağlıklı çocuklara göre istatistiksel olarak anlamlı daha kısaydı ($p<0,05$).
- Primer immün yetmezliği olan hastalarda sağlıklı çocuklara kıyasla ΔHR, HRmax, HR max (%), SBP (istirahat), Δ SBP, BF (istirahat) ve Δ BF parametreleri istatistiksel olarak anlamlı derecede azaldı ($p<0,05$). Primer immün yetmezliği olan hastalarda sağlıklı çocuklara kıyasla maksimum kalp hızı ve beklenen yüzde daha düşük, sistolik kan basıncı daha yüksek ve solunum frekansı daha yüksekti. HR (istirahat), SpO_2 (istirahat), ΔSpO_2, DBP (istirahat), ΔDBP, Dispne (istirahat), ΔDispne, Yorgunluk (istirahat), ΔYorgunluk, QF yorgunluğu (istirahat), ΔQF yorgunluk parametreleri gruplar arasında istatistiksel olarak benzerdi ($p >0,05$).
- Hastalarda istirahattaki RER, VO_{2kg}, HRR değerleri sağlıklı çocuklara göre daha düşük ve $EqCO_2$ daha yüksek olup istatistiksel olarak anlamlı fark vardı ($p<0,05$). VO_2, MET, HR, O_2HR, VCO_2, BF, EqO_2, SBP, DBP, dispne, yorgunluk, QF yorgunluk ve SpO_2 değerleri ise gruplar arasında istatistiksel olarak benzerdi ($p>0,05$).
- Aerobik eşikte, sağlıklı çocuklara kıyasla hastalarda RER, VO_{2kg} ve VE değerleri daha düşük, $EqCO_2$ ise daha yüksek olup istatistiksel olarak anlamlı fark vardı ($p<0,05$). VO_2, MET, HR, HRR, O_2HR, VCO_2, BF, EqO_2, SBP, DBP, dispne, yorgunluk, QF yorgunluk, SpO_2 ve iş yükü değerleri gruplarda istatistiksel olarak benzerdi ($p>0,05$).
- Hastalarda maksimalde, VO_{2kg}, MET, HR ve SpO_2 değerleri sağlıklı çocuklara kıyasla daha düşük $EqCO_2$, dispne, yorgunluk ve QF yorgunluk değerleri ise istatistiksel olarak daha yüksekti ($p<0.05$). RER, VO_2, VO_2%, VO_{2kg}, VO_{2kg}%, VE,

VE%, HR%, HRR, O_2HR, O_2HR%, VCO_2, BF, EqO_2, SBP, DBP ve iş yükü gruplarda istatistiksel olarak benzerdi (p>0.05). Altı (%42,85) hasta ve üç (%20) sağlıklı çocukta zirveVO_{2k}g, beklenen %80'den daha düşüktü. On üç (%93) hasta ve 15 (%100) sağlıklı çocuk maksimal kalp hızına ulaşmıştır. Bir hasta (%7) bacak yorgunluğu (M. Borg ölçeği (9 puan)) ve nefes darlığı (M. Borg ölçeği (6 puan)) nedeniyle egzersizi bitirmiştir. Testler sırasında hiçbir hastada veya sağlıklı çocukta ST-segment yükselmesi kaydedilmedi.

- Hastalarda aktif enerji harcaması, adım sayısı ve ortalama MET değerleri sağlıklı çocuklardan istatistiksel anlamlı olarak daha azdı (p<0,05). Toplam enerji harcaması, fiziksel aktivite ve yatatarak geçen süreleri gruplarda istatistiksel olarak benzerdi (p>0,05).
- Grupların günlük adım sayısına göre fiziksel aktivite düzeyi sınıflandırmaları istatistiksel olarak farklıydı (p<0.05). Sekiz (%57,1) hasta ve iki (%13,3) sağlıklı çocuk inaktif, bir (%7,15) hasta ve üç (%20) sağlıklı çocuk ise oldukça aktifti.
- Ortalama MET değerlerine göre fiziksel aktivite düzeyi sınıflandırmasında gruplar arasında istatistiksel bir fark yoktu (p>0,05). Tüm çocuklar ortalama MET değerlerine göre az aktifti.
- 6DYT sırasında, SmO_{2maks}, ΔSmO_2, $SmO_{2avg\text{-}maks}$ ve ΔSmO_{2avg} değerleri primer immün yetmezliği olan hastalarda sağlıklı çocuklara kıyasla istatistiksel olarak anlamlı şekilde azalmıştır. SmO_{2rest}, SmO_{2min}, $SmO_{2avg\text{-}min}$, $SmO_{2recovery}$, $SmO_{2recovery\text{-}avg}$, THb_{rest}, THb_{min}, THb_{max}, ΔTHb ve $THb_{recovery}$ değerleri gruplarda istatistiksel olarak benzerdi (p>0,05).
- Kardiyopulmoner egzersiz test sırasında kas oksijenasyonu, SmO_{2rest}, SmO_{2max}, $SmO_{2avg\text{-}max}$ ve $SmO_{2recovery\text{-}avg}$, ΔTHb değerleri sağlıklı çocuklara kıyasla PİY hastalarda istatistiksel olarak azalmıştır (p<0,05). SmO_{2min}, ΔSmO_2, $SmO_{2avg\text{-}min}$, ΔSmO_{2avg}, $SmO_{2recovery}$, THb_{rest}, THb_{min}, THb_{max}, ΔTHb ve $THb_{recovery}$ değerleri gruplar istatistiksel olarak benzerdi (p>0,05).
- Hastaların psikososyal sağlık, fiziksel sağlık boyutları ve anketin toplam puanları sağlıklı çocuklara kıyasla daha istatistiksel anlamlı olarak daha azdı (p<0,05).
- Primer immün yetmezliği olan hastalarda ebeveynlerin rapor ettiği psikososyal sağlık özet puanı, fiziksel sağlık özet puanı ve toplam puan sağlıklı çocuklara kıyasla istatistiksel anlamlı olarak daha azdır (p<0,05).

Tartışma

Bu çalışma birkaç önemli bulguyu ortaya koymuştur: PİY hastalarında fonksiyonel ve maksimal egzersiz kapasitesinde ve fiziksel aktivite düzeyleri azalmıştır, ve yaşam kalitesi kötüleşmiştir, üst ve alt ekstremite kas güçsüzlüğü ile submaksimal ve maksimal egzersiz testleri sırasında kas oksijenasyonu azalmıştır. Solunum fonksiyonları ve solunum kas kuvveti korunmuştur.

Sonuç ve Öneriler

Primer immün yetmezliği hastların maksimal ve fonksiyonel egzersiz kapasitesi, fiziksel aktivite seviyesi, solunum fonksiyonları, solunum ve periferik kas kuvveti, solunum kas enduransı, kas oksijenizasyonu, yaşam kalitesi ve dispnenin güvenilirliği, geçerliliği yüksek değerlendirme yöntemleriyle değerlendirilmesi ve sağlıklı çocuklarla karşılaştırılması hedeflenen çalışmamızın en önemli sonuçları;

Bulgularımız, primer immün yetmezliği olan çocukların fonksiyonel ve maksimal egzersiz kapasitesi, fiziksel aktivite seviyeleri, periferik kas kuvvetinde önemli azalmalar, kas oksijenizasyonunda azalmalar ve belirgin şekilde yaşam kalitesi azalmıştı. Bununla birlikte, solunum fonksiyonları, solunum kas kuvveti ve enduransı korunmuştur. Bu çalışma, objektif ölçümler kullanarak kapsamlı bir değerlendirme yapmasıyla öncü niteliktedir ve primer immün yetmezliği olan çocukların çok yönlü sağlık sorunlarına dikkat çekmektedir.

Çalışmamızın sonuçlarına göre önerilerimiz;

1. Çalışmamızda hastalarımızın yaş ortalaması küçük olmasına rağmen fonksiyonel ve maksimal egzersiz kapasitelesi, fiziksel aktivite düzeylerinde ve periferik kas kuvvetlerinde azalma olduğu görüldü. Kas oksijenizasyonunda anormallikler vardı ve yaşam kalitesi kötüleşti. Bu bulgular erken değerlendirme ve müdahalenin gerekliliğini vurgulamaktadır. Bu hastaların kapsamlı kardiyopulmoner rehabilitasyon programlarına dahil edilmesi, bu eksikliklerin giderilmesi ve genel sağlık sonuçlarının iyileştirilmesi açısından önemlidir. Rehabilitasyonun etkilerinin araştırılması gerekmektedir.
2. Araştırmamız, primer immün yetmezliği olan çocuklar ile sağlıklı çocuklar arasında yaş, boy, vücut ağırlığı, vücut kitle indeksi ve cinsiyet gibi demografik verilerde benzer dağılımlar olduğunu gösterdi, bu da örneklemimizin uygunluğunu ortaya koymaktadır.

3. Araştırmamızın sonuçları, PİY hastalarla sağlıklı çocuklar arasındaki solunum fonksiyon parametrelerinin istatistiksel olarak benzer olduğunu, PİY grubunda FEV_1/FV oranının anlamlı derecede düşük olduğunu gösterdi. Hastaların %28,57'sinde obstrüktif, %14,29'unda karma patern ve %7,17'sinde restriktif solunum fonksiyon anormalliği vardı. Bu bulgular, PİY çocuklarda obstrüktif solunum fonksiyon anormalliği yönelik bir eğilimi göstererek, pulmoner bakımının ihtiyacını vurgulamaktadır. PİY çocukların solunum fonksiyonlarının zaman içinde nasıl değiştiğini araştırmak için boylamsal araştırmaların yapılması gerekmektedir.
4. PİY hastalarla sağlıklı çocuklar arasında solunum kas kuvveti benzerdi ancak MEP (%) değerinin hasta grubunda daha düşük olduğunu göstermektedir. Özellikle hastaların %42,86'sının MİP'i ve %21,43'ünün MEP'i beklenenin %80'inden azdı. Solunum kas kuvvetinin düzenli olarak değerlendirilmesi, solunum kas zayıflık riskinin erken tespit edilmesine yardımcı olabilir. Bu hasta popülasyonunda inspiratuar ve ekspiratuar kas eğitiminin etkilerini anlamak için daha fazla çalışma yapılması gerekmektedir.
5. Çalışmamızın sonuçları PİY hastalarında solunum kas enduransının korunduğunu göstermektedir. PİY hastalarda solunum kas endurans zayıflığının varlığını, nedenlerini, solunum fonksiyonlarıyla ilişkisini ve İVİG tedavisiyle ilişkisini inceleyen ileri çalışmalara ihtiyaç vardır.
6. Çalışmamızda, PİY hastalarında ve sağlıklı çocuklarda periferik kas kuvveti objektif ölçümler kullanılarak değerlendirildi. Sonuçlar, hastalarda periferik kas kuvvetinin etkilendiğini göstermektedir. Zayıflığın nedenleri ve etkilerinin daha fazla araştırılması gerekmektedir. PİY çocuklarda periferik kas zayıflığının seyrini ve fonksiyonel sonuçlara etkisini araştırmak için boylamsal çalışmaların yapılması önerilmektedir.
7. Çalışmamız PİY hastalarda fonksiyonel egzersiz kapasitesinde azaldığını göstermektedir. Tüm hastaların (%100) ve altı (%40) sağlıklı çocuğun 6DYT mesafesi %80'inden kısaydı. Özellikle PİY hastalarda sağlıklı çocuklara kıyasla daha düşük maksimum kalp hızı ve beklenen yüzde, daha yüksek sistolik kan basıncı ve daha yüksek solunum frekansı görüldü. PİH hastalarında rutin olarak 6-DYT yapılması ve kardiyopulmoner rehabilitasyon programlarına dahil edilmelidir.
8. PİY hastaların maksimal egzersiz kapasitesi sağlıklı çocuklara göre daha düşüktür. Çalışmamız hastaların VO_2kg, MET, HR ve SpO_2 değerlerinin daha düşük olduğunu buldu. Ancak $EqCO_2$, Dispne, Yorgunluk ve QF yorgunluk algısı daha yüksekti.

Hastaların %42,85'inde ve sağlıklı çocukların %20'sinde zirve oksijen tüketimi beklenenin %80'inden daha düşüktü. Sonuçlar PİY hastalarla ilgili yeni araştırmaları ortaya çıkarmaktadır. Hastalığın solunum, kalp ve metabolik sistemler üzerindeki etkilerinin daha fazla araştırılması gerekmektedir.

9. Hasta ve sağlıklı çocukların fiziksel aktivite parametrelerinde anlamlı farklılıklar vardı. Hastaların fiziksel aktivite seviyesi azalmıştır Hastalarda aktif enerji harcaması, adım sayısı ve ortalama MET değerleri sağlıklı çocuklardan daha azdı. Toplam enerji harcaması, fiziksel aktivite ve yatatarak geçen süreleri gruplarda benzerdi. Ek olarak, grupların günlük adım sayısına göre fiziksel aktivite düzeyi sınıflandırmaları farklıydı; PİY hastalarının %57,1'i inaktifti. Objektif ölçümle fiziksel aktivitenin izlenmesi, fiziksel aktiviteye müdahale ve teşvik ihtiyacını gösterir. Bu hasta popülasyonu için programlar oluşturmak ve fiziksel aktivite danışmanlığı sağlamak kritik öneme sahiptir.
10. Altı-DYT ve KPET test sırasında quadriseps femoris kasının oksijenizasyonu, PİY hastaları ile sağlıklı çocuklar arasında anlamlı farklılıklar görülmektedir. Spesifik olarak, hastalarda maksimum kas oksijen saturasyonu sağlıklı çocuklara göre azalmıştır. Toplam hemoglobin düzeyleri gruplar arasında benzerdi. PİY'nin perfüzyon ve oksijen kullanımı üzerindeki fizyolojik etkilerini anlamak için gelecekteki çalışmaların yapılması gerekmektedir.
11. PİY çocuklar ve sağlıklı çocukların kendileri tarafından rapor edilen ÇİYKÖ anketi puanları, psikososyal sağlık, fiziksel sağlık yönleri ve genel puanlarda anlamlı farklılıklar gösterdi. Sağlıklı çocuklarla karşılaştırıldığında, PİY hastalarda yaşam kalitesinin azalmıştır. PİY hastaların ebeveynler tarafından rapor edilen psikososyal sağlık özet puanları, fiziksel sağlık özet puanları ve genel puanları sağlıklı çocuklara göre azalmıştır. PİY hastaların sorunlarını çözmek için multidisipliner bir yaklaşım uygulamalıdır. Bu çalışma mevcut literatüre bir ekleme niteliğindedir.

Limitasyonlar

Çalışmamızın sonuçlarını etkileyebilecek faktörlerden biri, İVİG tedavisi alması olabilir. Birkaç hasta, stabil tıbbi durumları nedeniyle İVİG tedavisi almamaktaydı. Dolayısıyla, ileride yapılacak çalışmalar İVİG tedavisi almayan hastaları dışlarlarsa daha spesifik sonuçlar elde edilebilir. Ek olarak, alt grup içindeki heterojenlik de sonuçları etkileyen başka bir sınırlama olabilir. Belirli alt gruplara odaklanan gelecekteki çalışmaların araştırılması gerekmektedir.

Bilim Kodu : 1024
Anahtar Kelimeler : Primer immün yetmezlik, egzersiz kapasitesi, fiziksel aktivite, yaşam kalitesi
Sayfa Adedi : 78
Danışman : Prof. Dr. Meral BOŞNAK GÜÇLÜ

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SYMBOLS AND ABBREVIATIONS

The symbols and abbreviations used in this study are presented below, along with their explanations.

Symbols	Explanations
%	Percentage
95%CI	95% Confidence Interval
<	less than
>	greater than
≤	less than or equal to
≥	greater than or equal to
cm	centimeters
cmH_2O	centimeter of water
min	minutes
dL	deciliter
g	gram
g/m^2	gram per square meter
Hz	hertz
IQR	interquartile range
kg	kilogram
kg/m^2	kilogram per sqaure meter
L	liter
m	meter
ml	milliliter
mm	millimeter
mmol/L	millimoles per liter
n	number of sample
N	Newton
Ng/mL	nanograms per milliliter
p	Statistical Probability of Error
s	seconds
x	Arithmetic mean

Symbols	Explanations
X±SS	Mean±Standard deviation
Δ	Pre-post test values
6-MWD	Six-minute walk distance
6-MWT	Six-minute walk test
ACCP	American College of Chest Physicians
ATS	American Thoracic Society
BF	breathing frequency
BMI	body mass index
BTK	Bruton's tyrosine kinase gene
CBC	complete blood count
CF	Cystic Fibrosis
CGD	Chronic Granulomatous Disease
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary exercise test
CVID	common variable immunodeficiency
DBP	Diastolic blood pressure
ENT	ear, nose, throat
$EqCO_2$	ventilator equivalent of carbon dioxide
EqO_2	ventilator equivalent of oxygen
ERS	European Respiratory Society
ESID	European Society of Immunodeficiencies
$FEF_{25-75\%}$	Forced expiratory flow between 25% and 75%.
FEV_1	Forced expiratory volume in one second
FEV_1/FVC	the ratio of forced expiratory volume in one second and forced vital capacity
FVC	Forced vital capacity
GVHD	graft-versus-host disease
HR	heart rate
HR-QOL	health-related quality of life
HRR	Heart rate reserve
HSCs	hematopoietic stem cells

Symbols	Explanations
HSCT	hematopoietic stem cell transplantation
IEI	Inborn Errors of Immunity
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IPEX	immune deficiency polyendocrinopathy
IVIG	Intravenous immunoglobulin
JMF	Jeffrey Modell Foundation
MEP	maximal expiratory pressure
MET	metabolic equivalent
MIP	maximal inspiratory pressure
NBT	nitroblue tetrazolium test
NGS	Next generation sequencing
NIRS	Near-Infrared Spectroscopy
O_2HR	oxygen pulse
PedsQL	Pediatric quality of life
PID	Primary immunodeficiency
QF	quadriceps femoris
RER	respiratory exchange ratio
SBP	systolic blood pressure
SCID	severe combined immune deficiency
SCIG	subcutaneous immunoglobulin
SD	standard deviation
SmO_2	muscle oxygen saturation
SmO_{2avg}	average muscle oxygen saturation
$SmO_{2avg-max}$	maximum average muscle oxygen saturation during test
$SmO_{2avg-min}$	minimum average muscle oxygen saturation during test

Symbols	Explanations
$SmO_{2avg\text{-}recovery}$	recovery average muscle oxygen saturation
SmO_{2max}	maximum muscle oxygen saturation during test
SmO_{2min}	minimum muscle oxygen saturation during test
$SmO_{2recovery}$	recovery muscle oxygen saturation
SmO_{2rest}	muscle oxygen saturation during rest
SpO_2	oxygen saturation
SPSS	Statistical Package for the Social Sciences
THb	Total hemoglobin
THb_{max}	maximum total hemoglobin during test
THb_{min}	minimum total hemoglobin during test
$THb_{recovery}$	recovery total hemoglobin
VCO_2	carbon dioxide output
VE	minute ventilation
VO_2	oxygen uptake
VO_2kg	oxygen uptake in kg
VO_2peak	peak oxygen uptake
W	work load
WAS	Wiskott-Aldrich syndrome
XLP	X linked lymphoproliferative disease

1. INTRODUCTION

Primary immune deficiencies (PIDs) encompass a diverse range of diseases arising from various abnormalities that impact the development, differentiation, and/or function of cells and components within the immune system. Clinically, PIDs are typified by an increased susceptibility to infections, autoimmune diseases, auto-inflammatory disorders, allergies, bone marrow failure, and/or malignancies. While each PID is individually rare, the collective number of individuals affected by these conditions represents a significant health burden [1].

The prevalence and distribution of PIDs vary among populations, with an estimated prevalence of 1/1.000 to 1/5.000 [2]. The prevalence of PIDs in Turkey is not well known due to the lack of extensive studies and a national registry system. However, a study encompassing two centers in Turkey reported a prevalence of 30.5/100.000 [3]. Currently, approximately 500 PID diseases have been identified [1], with selective immunoglobulin A (IgA) deficiency being the most common and common variable immunodeficiency (CVID) being the most common symptomatic PID [4].

Pulmonary complications are highly prevalent among patients with PID and significantly contribute to morbidity and mortality. Recurrent respiratory tract infections often serve as the initial warning sign in some PIDs and are a leading cause of mortality in adult patients with PID [5, 6]. The presence of two or more pneumonia episodes per year is considered one of the ten warning signs of PID [7]. Acute and chronic infections primarily constitute respiratory system diseases, while non-infectious respiratory complications include asthma, bronchiectasis, bronchiolitis obliterans, interstitial lung disease, granulomatous lung disease, and malignancies. These diseases significantly impact the quality of life of patients with PID, limit their working abilities, and restrict their physical and social activities [8, 9]. Delayed diagnosis and treatment of infections significantly impact the quality of life in patients with PID [10]. As survival from infections improves, non-infectious pulmonary complications become more common in patients with PID [11, 12]. Particularly in PIDs characterized by antibody deficiencies, permanent lung damage is observed in 20-40% of patients [13]. Physical activity levels are also affected in Patients with PID, however there are only survey studies on this topic [14]. Therefore, it is expected that respiratory muscle strength, as well as respiratory muscle endurance, functional exercise capacity, and peripheral muscle strength, would be affected in these patients. However, no information is available on

maximal exercise capacity, functional exercise capacity, respiratory muscle strength and endurance, and peripheral muscle strength.

This study aims to compare the maximal exercise capacity, functional exercise capacity, pulmonary function, physical activity level, quality of life, respiratory muscle strength and endurance, peripheral muscle strength, muscle oxygenation, and dyspnea in children with PID and healthy children.

This study will assess various aspects of health and activity in children with primary PID compared to healthy children. Exercise capacity and physical activity level are the primary outcomes. Exercise capacity will be evaluated through two methods: maximal exercise capacity (VO_2peak) using a cardiopulmonary exercise test (CPET) and functional exercise capacity using the distance walked during a 6-minute walk test (6-MWT). Additionally, physical activity levels will be monitored using a multi-sensor physical activity monitor.

Secondary outcomes include muscle oxygenation measured by Near-Infrared Spectroscopy (NIRS), pulmonary function assessed by spirometry, and the strength and endurance of both respiratory muscles (measured by maximal inspiratory pressure and increasing threshold load endurance test) and peripheral muscles (measured by digital handheld dynamometer). Lastly, children's quality of life will be evaluated using the PedsQL questionnaire, and dyspnea and fatigue will be assessed through the Modified Borg Scale. This comprehensive approach will allow us to compare children's health and activity levels with PID to healthy controls.

Hypothesis of the study

Hypothesis for the primary outcomes:

H_0: There is no significant difference in maximal exercise capacity, functional exercise capacity, and physical activity levels between children with PID and healthy children.

H_1: There is a significant difference in maximal exercise capacity, functional exercise capacity, and physical activity levels between children with PID and healthy children.

Hypothesis for the secondary outcomes:

H_0*:* There is no significant difference in pulmonary function, respiratory muscle strength, respiratory muscle endurance, peripheral muscle strength, muscle oxygenation, quality of life, dyspnea, and fatigue between children with PID and healthy children.

H_1*:* There is a significant difference in pulmonary function, respiratory muscle strength, respiratory muscle endurance, peripheral muscle strength, muscle oxygenation, quality of life, dyspnea, and fatigue between children with PID and healthy children.

2. GENERAL INFORMATION

2.1. Primary Immunodeficiency

Primary immunodeficiencies (PIDs) constitute a diverse group of disorders. These disorders arise from abnormalities that disrupt the development, specialization (differentiation), and/or function of immune system cells and components. Clinically, PIDs manifest as an increased susceptibility to infections. However, the spectrum of complications extends beyond infections, encompassing autoimmune diseases, auto-inflammatory disorders, allergies, bone marrow failure, and even malignancies. While each PID is uncommon, the collective number of individuals affected by these conditions represents a significant public health burden [15].

The immune system is a highly developed network of organs and cells that work together to protect individuals against internal threats like cancer and infectious microorganisms. In addition, the immune system consists of specialized cells, tissues, proteins, and organs. Its main constituents include phagocytic cells, complement, and B- and T-lymphocytes. These elements play distinctive and essential roles in the immune defense mechanism. Immunodeficiency can be acquired (secondary) or congenital (primary), resulting from the absence or failure of a component of the immune system. Environmental factors, including HIV infection, chemotherapy, radiation, malnutrition, and other external impacts, can lead to the development of secondary immunodeficiency disorders. Primary immunodeficiency diseases (PIDs), on the other hand, are inherited conditions caused by specific gene mutations [15]. Nonetheless, in the vast majority of times, they result in an unnaturally elevated vulnerability to infections as well as a propensity to autoimmune disorders and cancers. PIDs were first identified in 1952 by Bruton. Bruton reported a young boy who had recurrent pneumonia, no serum gamma globulins, and recovered after receiving gamma globulins intramuscularly [16]. This type of agammaglobulinemia is called Bruton's syndrome or X-linked agammaglobulinemia. Two years prior, Glanzmann and Riniker had reported a newborn with severe lymphopenia and lymphoid tissue atrophy that died infections [17]. Later, Hitzig reported other infants with early-onset life-threatening infections who were deficient in both gamma globulins and lymphocytes [18]. This condition is now referred to as severe combined immune deficiency (SCID) [19]. A few years later, the identification of T and B cells was made possible by the combined demonstration of the

significance of humoral and cellular immunity in fighting infections, which was made possible by isolated agammaglobulinemia and SCID [20]. Innate immunological inborn errors were the first to be documented in the 1950s, whereas complement inborn errors were first noted in the 1960s. The arm of immunity that is compromised (T lymphocytes, B lymphocytes, phagocytes, complement) largely determines the type of pathogens (viruses, bacteria, fungi, or parasites, "opportunistic" or not) that cause infections in patients with PID. Susceptibility to various infections has long been used to characterize PIDs, regardless of category. Even though agammaglobulinemia, SCID, and CGD are clinically and immunologically homogenous types of PIDs that are transmitted differently (X-linked, autosomal recessive) [21]. Autoimmunity, autoinflammation, allergy, and cancer are typical depending on the specifics of the disease [22]. The wide range of phenotypes associated with these disorders has been proposed to be referred to as "inborn errors of immunity" (IEI). Most importantly, advances in molecular genetics and cellular immunology have allowed for much more precise classification of the many forms of IEI. The International Union of Immunological Societies Committee on Inborn Errors of Immunity's 2020 categorization lists 485 IEI, an increase from the previous year because of next-generation sequencing (NGS) [1].

Currently, IEIs are divided into ten tables, each with a sub-table that divides groupings of diseases into overlapping phenotypes [2]. These tables list the following conditions: 1. Combined Immunodeficiencies; 2. Combined immunodeficiencies with syndromic features; 3. Predominantly antibody deficiencies; 4. Diseases of immune dysregulation; 5. Congenital defects of phagocytes; 6. Defects in intrinsic and innate immunity; 7. Autoinflammatory diseases; 8. Complement deficiencies; 9. Bone marrow failure; 10. Phenocopies of inborn errors of immunity. The listing is given in table number 2.1.

Table 2.1. The classification of inborn errors of immunity based on The International Union of Immunological Societies Committee on Inborn Errors of Immunity [2]

Inborn Errors of Immunity classification	
1.	Combined Immunodeficiencies;
2.	Combined immunodeficiencies with syndromic features
3.	Predominantly antibody deficiencies
4.	Diseases of immune dysregulation;
5.	Congenital defects of phagocytes;
6.	Defects in intrinsic and innate immunity;
7.	Autoinflammatory diseases;
8.	Complement deficiencies;
9.	Bone marrow failure;
10.	Phenocopies of inborn errors of immunity.

2.2. Epidemiology

Epidemiological studies show considerable regional and racial differences in the prevalence and pattern of immunodeficiency diseases. In the general population, the prevalence of PIDs is unknown. Although the global incidence of these diseases is believed to be 1:10.000, it varies differently throughout countries due to social customs, environmental factors, genetic background, and access to healthcare. Many registries have been established in different countries to provide information about the epidemiology, prevalence, and management of PIDs. Among the most known registries are the European Society for Immunodeficiencies (ESID), the Clinical Immunology Society, Latin American Society for Immunodeficiencies, the Asia Pacific Society of Immunodeficiencies, and the African Society for Immunodeficiencies. Among these, ESID is the largest online registry that contains clinical and laboratory information on patients with PID. Turkey has no national registry of PIDs, so it is harder to state an exact number in the general population. A study done in 2007 in the USA reported a prevalence of 1:1.200, suggesting that PIDs might not be as rare as they are thought to be [23]. The online ESID registry is the largest, containing clinical and laboratory information. As of the latest report done in October 2023, the number of new registry patients was 30.765 [24].

In Turkey, no studies give nationwide prevalence data, but a two-center study reported a prevalence of 30.5/100.000, and most patients were predominantly antibody immunodeficiency [3]. Moreover, one study done in 2011 reported a prevalence of IgA deficiency patients as 1:188 [25] and a regional study determined SCID incidence as 1/10.000 [26].

2.3. Clinical Manifestations

Several warning signs have been developed to increase awareness about the early diagnosis of PIDs. The 10 warning signs of primary immunodeficiencies as defined by the Jeffrey Modell Foundation (JMF) are the most commonly used ones. In children admitted with frequent infections, a detailed history should be taken and the 10 warning signs of PID described by the JMF should be assessed in addition to a full physical examination [27].

Ten warning signs based on JMF are:

1- Four or more new ear infections within one year.

2- Two or more serious sinus infections within one year.

3- Two or more months on antibiotics with little effect.

4- Two or more pneumonia within one year.

5- Failure of an infant to gain weight or grow normally.

6- Recurrent, deep skin or organ abscesses.

7- Persistent thrush in the mouth or fungal infection on the skin.

8- Need for intravenous antibiotics to clear infections.

9- Two or more deep-seated infections, including septicemia.

10- A family of PID.

Infections are one of the most well-known and closely linked symptoms of PIDs. However, the number of non-infectious disease presentations is also rising. Depending on the immune defect, the organ systems affected vary as well. Most patients suffer from recurrent or opportunistic infections, frequently encountering bacterial septicemia, sinus infections, and recurrent respiratory infections. Encapsulated bacteria such as *Streptococcus pneumoniae*

and *Haemophilus influenzae* type b are attributed to the causes [28]. Typically, the earliest warning symptoms of PIDs are respiratory infections, which are the most prevalent sign. Their vast manifestations can be presented in acute or chronic infections [11, 12]. The upper respiratory conditions are rhinosinusitis, otitis media, and pharyngitis [29]. Lower respiratory tract infections are pneumonia, bronchitis, bronchiectasis, interstitial lung disease, and bronchiolitis obliterans [30-32]. Moreover, patients also suffer from gastrointestinal manifestations such as chronic diarrhea, infectious colitis, and inflammatory bowel syndrome. Patients also suffer from skin infections such as abscesses and pyodermitis [33, 34].

Alongside infections, autoimmunity and inflammatory conditions are common in many PIDs. Hematologic cytopenias, hepatitis, vitiligo, villous atrophy, autoimmune neutropenia, polyendocrinopathy, and enteropathy are among the most prevalent autoimmune manifestations [35]. In common variable immunodeficiency (CVID), progressive lung lymphocytic and/or granulomatous infiltrates are frequently observed [36]. Mild eczema is seen in most PIDs; other inflammatory skin conditions seen are alopecia, urticaria, psoriasis, erythroderma, vitiligo, and ectodermal dystrophy [37].

In conjunction with infections and autoimmunities, malignancies represent predominant clinical presentations observed in many forms of PIDs. Although the incidence of PIDs can be high, each genetic subtype is rare, so data regarding PIDs' malignancies are lacking. The main causes of PIDs linked to cancers are gene abnormalities controlling DNA repair, apoptosis, the cell cycle, and bone marrow maturation [38]. Ataxia-telangiectasia, Wiskott-Aldrich syndrome, CVID and DOCK8 deficiency are the most frequent PID in patients with malignancy [39]. Along with Hodgkin lymphoma and leukemia in certain subtypes, non-Hodgkin lymphoma is the most prevalent malignancy observed in patients with PID [40].

2.4. Diagnosis

The hallmark of PIDs is infection, but many other factors must be considered to diagnose correctly. In addition to infections, a variety of conditions can cause PID suspension, including eczema, diarrhea, immunization side effects, unexplained bronchiectasis, lack of immune tissues, delayed umbilical cord shedding, and aberrant hair growth. PIDs typically manifest as one of the eight distinct clinical symptoms listed below [41, 42].

Eight characteristic clinical signs of PIDs

1. Recurrent ENT (ear, nose, throat) and airway infections
2. Failure to thrive from early infancy
3. Recurrent pyogenic infections
4. Unusual infections or unusually severe course of infection
5. Recurrent infections with the same type of pathogen
6. Autoimmune or chronic inflammatory disease and/or lymphoproliferation
7. Characteristic combination of clinical features in eponymous syndromes
8. Angioedema

The history and physical examination are essential initial assessments for the physician to decide if more testing is necessary. Among the laboratory tests used are complete blood count (CBC), peripheral blood smear, serum immunoglobulin levels (IgG, IgA, IgM and IgE), Lymphocyte Subsets, complement levels, nitroblue tetrazolium (NBT) test, dihydrorhodamine (DHR) test, T-cell proliferation assay, genetic testing, bone marrow examination and specific functional tests (phagocytosis assays for neutrophil function or assays for cytokine production) [42].

2.5. Treatment

2.5.1 Immunoglobulin Replacement Therapy
2.5.2 Hematopoietic Stem Cell Transplantation
2.5.3 Gene therapy

2.5.1. Immunoglobulin Replacement Therapy

Intravenous immunoglobulin (IVIG) is a combination of immunoglobulins that have been pooled from healthy donors, depending on the manufacturer. When plasma cells respond to different antigenic stimuli involved in a variety of physiological and pathological processes, they produce immunoglobulins, or antibodies. Immunoglobulins are mainly responsible for the adaptive arm of the immune system. They include IgM, IgG, IgD, IgA, and IgE [43]. IgG makes up between 75 and 80% of all immunoglobulins and has a plasma concentration range of 700 to 1600 mg/dL. Treatment for PID patients appears to need IVIG replacement therapy since these patients are unable to generate an effective immune response to infections [44]. Thus, the objective of IVIG therapy is to restore sufficient IgG antibodies to

either opsonize or passively destroy a broad spectrum of infectious microorganisms or to initiate an active immune response by stimulating distinct immune cells, so safeguarding against a range of illnesses. IVIG provides passive immunity by neutralizing viruses and bacterial toxins, acting as an IgG replacement. Through a particular interaction with pathogens, they also assist in low-dose activation of the complement cascade [45]. For instance, IVIG causes B cell immunoglobulin synthesis, dendritic cell (DC) maturation, and T cell immunity modulation in PIDs, boosting CD4 levels in patients with CVID [46-48].

Immunoglobulin replacement therapy can be administered at a low or high dose. IVIG is typically given as low-dose replacement therapy for PIDs every three to four weeks at a rate of 400 to 600 mg/kg. It has been demonstrated to lower infection frequency, lung complications, antibiotic use, and hospital stay duration [49, 50] . Immunoglobulin replacement therapy is most commonly administered intravenously (IVIG) but can also be administered subcutaneously (SCIG). SCIG treatment may be taken into consideration if there are systemic adverse effects and insufficient venous access. Usually, SCIG is given considerably more frequently—every week or every two weeks—and at a much lower dosage. Its minimal transfusion volume, home administration benefit, and better patient compliance [51] .

2.5.2. Hematopoietic Stem Cell Transplantation

Hematopoietic cells' inherent genetic flaws cause the majority of PIDs. Consequently, using healthy donor hematopoietic stem cells (HSCs) to replace mutant cells is a therapeutic strategy. Allogeneic hematopoietic stem cell transplantation (HSCT) is a therapy that can save lives in cases of highly life-threatening illnesses. A patient's unique traits must be considered when making decisions on the indication and timing of a transplant, in addition to carefully weighing the hazards of HSCT against the likelihood of future disease progression [52]. HSCT can be carried out using a compatible unrelated donor or a somewhat less compatible related donor in situations where an ideal donor is unavailable.

In contrast, an optimally matched sibling donor is the preferred option. Improvements in donor conditioning, preparing protocols, and handling difficulties after transplantation enable this adaptability. The reported survival rates for newborns diagnosed with SCID indicate a 90% success rate when a compatible relative donor is available, 70% when relying on compatible unrelated donors, and a range of 70-80% for patients without SCID [53].

2.5.3. Gene therapy

Gene therapy represents a novel approach to treating PIDs. More advanced therapeutic options have surfaced as clinical knowledge about the underlying causes of these disorders develops and technology progresses. Previously, HSCT was often considered the final resort for treating various forms of PIDs despite its effectiveness for many patients. However, disparities between the hematopoietic stem cells (HSCs) of the donor and the patient might result in graft-versus-host disease (GVHD) consequently increasing morbidity and mortality rates. Gene therapy offers a promising alternative by genetically correcting the patient's autologous HSCs by employing gene editing methods or viral vectors for gene addition to return function to normal. Gene therapies are actively advancing for the treatment of PIDs. Among these conditions: chronic granulomatous disease (CGD), leukocyte adhesion deficiency-I (LAD-1), Wiskott-Aldrich syndrome (WAS), some forms of SCID, immune deficiency polyendocrinopathy (IPEX) and X linked lymphoproliferative disease (XLP) [54].

2.6. Rationale for Pulmonary Rehabilitation in Patients with Primary Immunodeficiency

2.6.1. Primary Immunodeficiency and Pulmonary Function Test

Patients with PID are more prone to infections, particularly infections of the respiratory system. These repeated respiratory infections can cause long-term inflammation and anatomical alterations in the airways [55]. This ongoing inflammation often results in lung complications, with bronchiectasis being the most common. Consequently, assessing lung function becomes crucial for patients with PID. Studies have shown that chronic airway inflammation affects 20-40% of these patients. While research on pulmonary function in PID exists, it focuses more on adults than children [13, 56, 57].

Declining pulmonary function measures might result from progressive structural damage to the lungs caused by non-infectious inflammation, recurrent respiratory infections, and interstitial lung involvement. Moreover, studies show that IgG levels and lung functions correlate. Patients with low serum levels of IgG have worse lung function, and FEV_1 deteriorates faster [58]. Studies demonstrate a progressive decline in lung function, FEV_1 and FVC being the most affected, which worsens with age [55]. The reduction in exercise capacity, peripheral muscle strength, and quality of life in children with PID may be caused

by airflow obstruction and air trapping in the lungs associated with bronchiectasis. However, there are no studies regarding it. Therefore, evaluating lung function in patients with PID is critical for early detection of complications and improving their overall health outcomes.

2.6.2. Primary Immunodeficiency and Respiratory Muscle Strength and Endurance

Respiratory muscles are crucial in air movement and blood flow throughout the body. Many respiratory diseases are associated with the development of respiratory muscle weakness. This weakness can then impact respiratory gas exchange, leading to hypoxemia and hypercapnia. Compromised respiratory muscle function further impedes effective expiration, causing difficulties with exertion, coughing, and clearing mucus from the airways [59]. No research evaluated respiratory muscle strength and endurance in patients with PID.

Frequent respiratory infections can damage lung tissues through inflammation and scarring. Further respiratory complications lead to chronic lung complications like bronchiectasis and COPD, impairing the airflow and increasing the workload of the respiratory muscles. Reduced respiratory muscle strength can have significant consequences in patients with PID, including shortness of breath, fatigue, and difficulty clearing the mucus from the airway, leading to lower exercise capacity and increasing morbidity and mortality [60, 61].

2.6.3. Primary Immunodeficiency and Peripheral Muscle Strength

Primary immunodeficiencies (PIDs) can extend their impact beyond the respiratory system, affecting skeletal muscles throughout the body and leading to peripheral muscle weakness. This weakness can manifest in various ways and significantly impacts the quality of life for individuals with PIDs [60, 61].

The exact mechanisms underlying muscle weakness in PIDs remain under investigation. However, insights can be drawn from similar conditions like bronchiectasis, chronic obstructive pulmonary disease (COPD), and cancers. These conditions share common factors like chronic inflammation, oxidative stress, nutritional deficiencies, altered cytokine levels, and protein imbalances, all contributing to the decline in the function and strength of muscles [62]. For instance, deconditioning brought on by a reduction in physical activity appears to be a major factor in peripheral muscle dysfunction in people with COPD [63, 64].

Moreover, patients with bronchiectasis and airway obstruction had upper and lower limb muscle weakness, specifically females with lower quadriceps muscle strength [61, 65].

Muscle weakness and respiratory insufficiency in limb muscles, especially the lower extremities, can result in prolonged under-loading and inactivity. This inactivity reduces muscle mass, especially type-I muscle fibers [66, 67]. No studies have evaluated peripheral muscle strength in patients with PID. This study will utilize a handheld dynamometer for objective assessment of upper and lower extremity strength in this patient group.

2.6.4. Primary Immunodeficiency and Exercise Capacity

Patients with PID can often face challenges when it comes to exercise capacity. While exercise is crucial for overall health, several factors associated with PIDs can limit a person's ability to engage in physical activity. Recurrent infections, complications of respiratory infections such as bronchiectasis, pneumonia, lung abscesses, and empyema, along with structural airway abnormalities, cause shortness of breath, fatigue, coughing, muscle weakness, and psychological factors, all of which limit participation in exercise and physical activity [12, 68]. These factors can significantly impact the exercise capacity. Although there is some research on exercise perception in adult patients with PID, data related to children is limited [69].

The cardiopulmonary exercise capacity test (CPET) is the golden standard for measuring maximal exercise capacity. CPET offers comprehensive insights into physiological limitations. These limitations can originate from the respiratory and cardiovascular systems. Gas exchange abnormalities, such as reduced diffusion capacity or ventilation inefficiency, can limit oxygen delivery to working muscles [70-72]. Additionally, impaired lung function, a common complication in some PIDs (e.g., bronchiectasis), can restrict airflow and contribute to exercise intolerance.

Moreover, dysfunction in oxygen uptake can be limited by cardiac output or peripheral vascular insufficiency [12]. No study evaluates oxygen uptake in this patient population. Despite the ongoing debate surrounding its classification within Inborn Errors of Immunity (IEI), Cystic Fibrosis (CF) is a valuable reference point for studying exercise capacity and oxygen uptake in patients with PIDs. Research has demonstrated a correlation between

decreasing peak VO_2 and increased mortality in CF patients [72]. This finding suggests that evaluating peak VO_2 in patients with PID is very important.

Another valuable method for measuring functional exercise capacity is the 6-minute walk test (6-MWT). The functional exercise level for everyday physical activities may be better reflected by this test since most activities of daily life are carried out at submaximal effort levels. Six-MWT is easily applicable and does not require much equipment [73]. Impaired exercise capacity can be expected due to PID, but more research is needed. Existing literature lacks evaluation of either maximal or functional exercise capacity in this patient population.

2.6.5. Primary Immunodeficiency and Physical Activity

Children with chronic diseases exhibit distinct pathophysiological characteristics that impact their exercise tolerance and physical activity levels [74]. The combination of factors like recurrent infections, inflammation, autoimmunity, and malignancy impact the physical activity in patients with PID. According to the World Health Organization (WHO), children should engage in moderate-to-intense physical exercise for 60 minutes per day [75]. Frequent infections and hospitalization make way for physical deconditioning, making it harder for the patients to engage regularly in exercise activities. Moreover, poor lung function limits aerobic capacity and makes physical activity more challenging, resulting a vicious cycle of inactivity and further deconditioning [74, 76]. In the literature, no research measures the physical activity levels of patients with PID. The application of a metabolic Holter device for physical activity measurement in this patient population has not been previously reported.

2.6.6. Primary Immunodeficiency and Muscle Oxygenation

Recurrent infections, chronic inflammation, malignancy, and autoimmunity combined in PID can have an impact on muscle oxygenation. Although muscle oxygenation in PID has not been studied specifically, it can be implied based on the studies regarding the mechanisms of mitochondrial dysfunctions in autoimmunities [77]. In chronic diseases, the muscle oxidative capacity is impaired by many factors like inflammations, hypoxia, and physical inactivity [78]. The vicious cycle of recurrent infections and chronic inflammation fuels oxidative stress, damaging blood vessels and mitochondria. This combined effect impairs oxygen delivery and utilization within muscles. Additionally, immune dysregulation

in PIDs disrupts endothelial cell function and reduces capillary density in muscle tissue, further compromising oxygen perfusion [76, 79].

In this study, muscle oxygenation is measured in the quadriceps muscle using a Moxy monitor during the cardiopulmonary exercise (CPET) and the six-minute walk test (6-MWT). The muscle oxygenation measurements are taken before the start of the test, throughout the test, and during recovery. As the body's oxygen demand increases during activity, oxygen from the capillaries is rapidly utilized by the mitochondria in the muscles. Consequently, muscle oxygen saturation is expected to be low when measured with the Moxy® monitor during exercise [80]. The Moxy® monitor will be used for the first time to evaluate muscle oxygenation in patients with PID. Additionally, the measurements taken during CPET and the 6-MWT will be novel, contributing valuable data to the literature.

2.6.7. Primary Immunodeficiency and Quality of Life

Patients with PID frequently experience limits in their everyday activities and a significant reduction in their health-related quality of life (HR-QOL) when compared to healthy individuals. The ongoing presence of symptoms, complications, and recurring infections, in addition to the financial and physical demands of therapy, all play a part in this reduction in HR-QOL. Compared to healthy controls, it is significantly lower [81-84].

There is currently no disease-specific questionnaire for PID that assesses the quality of life in the pediatric population. Additionally, limited research has been conducted on developing disease-specific HR-QOL questionnaires for adults [8, 85, 86]. A variety of questionnaires, including the 36-item Short Form Health Survey (SF-36), the Pediatric Quality of Life Inventory (PedsQL), the Strengths and Difficulties Questionnaire (SDQ), the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L), and the Quality of Life Index (QLI), have been used to evaluate the quality of life for pediatric PID patients. Study findings showed that quality of life decreased in patients with PID [84]. The Pediatric Quality of Life Inventory (PedsQL), which has validity and reliability in Turkish, was used in our study to assess the quality of life [87-89]. The results will contribute to the existing literature.

3. MATERIAL AND METHODOLOGY

The study was conducted at Gazi University, Faculty of Health Sciences, Department of Cardiopulmonary Physiotherapy and Rehabilitation. Patients with primary immunodeficiency who were referred for cardiopulmonary rehabilitation from Dr. Sami Ulus Hospital the Pediatric Immunology and Allergy Diseases Department and healthy children were included. This study aimed to compare maximal exercise capacity, functional exercise capacity, pulmonary function, physical activity level, muscle oxygenation, respiratory muscle strength and endurance, peripheral muscle strength, and quality of life in children with primary immunodeficiency and healthy controls.

3.1. Participants

Between **May/2023 and the May/2024**, patients diagnosed with primary immunodeficiency at Dr. Sami Ulus Children Health and Diseases Training and Research Hospital, Pediatric Immunology and Allergy Diseases Department were referred for rehabilitation at Gazi University, Faculty of Health Sciences, Cardiopulmonary Physiotherapy and Rehabilitation Unit. In the study, 14 patients and 15 age and gender-matched healthy controls were included. Notices detailing the research were posted on university entrance doors to recruit healthy children for the study. Children who expressed interest by contacting the provided phone numbers were then invited to participate.

3.1.1. Inclusion criteria for patients:

- Patients with primary immunodeficiency diagnosis based on European Society for Immunodeficiencies (ESID) diagnostic clinical criteria [90, 91].
- Patients aged 6 to 18 years old, of both genders
- Patients with stable clinical condition

3.1.2. Exclusion criteria for patients:

- Those with conditions impeding physical activity (e.g., orthopedic, neurological, or psychological limitations).

- Individuals presenting with acute infections during evaluation or within the last month

3.1.3. Inclusion criteria for healthy controls:

- Individuals between the ages of 6-18
- Those who want to participate in the study voluntarily

3.1.4. Exclusion criteria for healthy controls:

- Individuals with any diagnosed disease
- Those with acute infection at the time of evaluation or within a month

3.2. Study Design

The study design was planned as cross-sectional. Patients with PID who received regular medical examinations, diagnoses, radiological follow-ups, laboratory tests, and treatment from immunologists who were referred for cardiopulmonary rehabilitation were included in the study. The evaluation took place over two days at Gazi University, Faculty of Health Sciences, Cardiopulmonary Physiotherapy and Rehabilitation Unit. On the first day, patients and healthy controls underwent assessments for pulmonary function, respiratory and muscle strength, functional exercise capacity, and respiratory muscle endurance. On the second day, their maximal exercise capacity and quality of life were assessed. The maximal exercise capacity was determined through CPET, while functional exercise capacity was assessed using 6-MWT. Muscle oxygenation was monitored using the "Moxy® monitor," and physical activity level was tracked using a multi-sensor physical activity monitor. Pulmonary function was measured using a spirometer. In addition, respiratory muscle strength was evaluated with a mouth pressure device, and respiratory muscle endurance was assessed using an increasing threshold load endurance test. Peripheral muscle strength was evaluated with a portable digital handheld dynamometer. The quality of life was evaluated using the Pediatric Quality of Life Inventory™ 4.0 (PedsQL™ 4.0), and levels of dyspnea and fatigue were determined using the Modified Borg Scale.

The study was accepted by the Gazi University Clinical Research Ethics Committee on 04.04.2023 (Decision no: 464) (Attachment 1). The scope and purpose of the study were

explained to the children and their families who participated in the study, and they signed an informed consent form (Attachment 2). ClinicalTrials.gov ID: NCT05999422

3.2.1. Evaluation of the Subjects

During the study, demographic characteristics of both patients and healthy individuals were recorded. Height was measured in meters (m) and weight in kilograms (kg). The body mass index (BMI) was computed by dividing the weight (kg) by the square of the height (m^2), and the resulting BMI values were recorded. A detailed medical history was obtained from both the individual and their family including recording the age of symptom onset and diagnosis, personal medical history, comorbidities, current medications, smoke exposure, weight fluctuations and eating difficulties, family history of consanguineous marriage, educational background, exercise habits, physical examination, laboratory work, radiological findings, histopathological findings and genetic test.

3.2.2. Evaluation of Symptoms

A detailed pulmonary health history was obtained from the participants. This included inquiries about cough (productive or non-productive, daytime or nighttime), sputum production, dyspnea, hemoptysis and orthopnea. The severity and circumstances of dyspnea were asked, focusing on both rest and exertion dyspnea, as well as activities that trigger exertion dyspnea.

3.2.3. Pulmonary Function Test

The pulmonary function test is conducted following the criteria set by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) using a portable spirometer device (Cosmed, Class II/ Internally Powered Equipment, Italy) [92]. The test was conducted while the subject was seated upright and with their nostrils closed with a nose clipper. The measured pulmonary function test parameters are: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), the ratio of forced expiratory volume in one second and forced vital capacity (FEV_1/FVC), peak expiratory flow (PEF), and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75\%}$). The best of three technically acceptable maneuvers, with 95% compliance, was recorded for statistical analysis.

Pulmonary function test parameters were recorded as liters (L) and percentage of expected values according to age, gender, weight, and height [92-94].

3.2.4. Respiratory Muscle Strength

Respiratory muscle strength was evaluated using a portable electronic oral pressure measurement device (Micro Medical MicroRM, UK), following ATS/ERS criteria [95]. Maximum inspiratory pressure (MIP) measurements were obtained during the Müller maneuver (inspiration with the nose closed), executed through the mouth using a pressure measuring device. Maximum expiratory pressure (MEP) was acquired during the Valsalva maneuver (forced expiration). These measurements were taken while the patient sat upright on a chair without back support, with the nose closed with a nose clip. MIP was measured at residual volume after maximum expiration, involving rapid and forceful inspiration. Rapid, deep expiration at total lung capacity following maximum inspiration was performed for MEP measurement. Patients were instructed to sustain a strong effort for at least two seconds during these maneuvers and were encouraged with specific cues. Each measurement was repeated at least seven times, and pressures were recorded in centimeters of water (cmH_2O). The measurement was repeated if consecutive measurements differed by more than 5% or 5 cmH_2O. The highest MIP and MEP values were selected for statistical analysis [96]. MIP and MEP measurements were evaluated using Domenech-Clar et al. [97] reference equations.

Males: MIP (cmH_2O): -27.020 – (4.132 x age) - (0.003 x height (cm) x weight (kg))

Males: MEP (cmH_2O): 7.619 + (7.806 x age) + (0.004 x height (cm) x weight (kg))

Females: MIP (cmH_2O): -33.854 – (1.814 x age) - (0.004 x height (cm) x weight (kg))

Females: MEP (cmH_2O): 17.066 + (7.22 x age)

3.2.5. Respiratory Muscle Endurance

Respiratory muscle endurance was evaluated with an inspiratory muscle training device (Power Breathe®, HaB International Ltd. Southam, England) with increasing threshold loading respiratory muscle endurance test. The patient was seated upright for the test, and a nasal clip was used to keep their nostrils shut. The evaluation started with 20% of the MIP

value and the inspiratory threshold load was increased by 20% of the MIP value every two minutes. The pressure was increased without removing the device from the mouth. The respiratory muscle endurance value was calculated by multiplying the total test time by the maximum pressure value sustained for at least one minute. Oxygen saturation of the patients was evaluated with a portable pulse oximeter (Model 9590 Oximeter Nonin® Medical, Inc, Plymouth, MN, USA), and shortness of breath was evaluated with the Modified Borg scale before the start of the test and before and after each resistance increase. One of the test termination criteria was when the patient could not take three consecutive deep breaths or developed extreme shortness of breath or severe fatigue [98]. Using the reference equation developed by Woszezenki et al., the percentage of predicted results for the respiratory endurance test was calculated based on age [99].

Inspiratory muscle endurance (cmH_2O): -23.861 + (MIP (cmH_2O) x 0.654) + (age x 1.493)

3.2.6. Peripheral Muscle Strength

The isometric muscle strength of shoulder abductors and knee extensors was assessed using a portable hand dynamometer (JTECH PowerTrack Commander, Baltimore, USA). The patient's shoulder abductor strength was evaluated in an upright sitting position without support, with the arm at a 90º abduction, and knee extensor strength was assessed in an upright sitting position with the knee at a 90º extension. Each test was conducted three times on both the right and left sides, with the individual required to maintain maximum effort for at least five seconds. Measurements were recorded in Newton (N), and the highest recorded value was chosen for analysis. The anticipated muscle strength value was computed using the reference equation proposed by Beenakker et al. [100].

3.2.7. Functional Exercise Capacity: Six-Minute Walk Test

The Six-Minute Walk Test has been used to assess functional exercise capacity in accordance with the ATS and ERS requirements. The test was conducted on a 30-meter-long corridor; with two cones marking the beginning and finish of the test. It was repeated twice on the same day with a 30-minute break in between [101]. Before commencing the tests, patients were given a 10-minute rest period to establish a baseline condition. The patient's heart rate, blood pressure, oxygen saturation, respiratory rate, dyspnea, fatigue, and leg fatigue perception were recorded before and after the test and at the 1st minute of recovery.

In the context of these measurements, heart rate was recorded using a heart rate monitor (Polar FTI00, China), blood pressure was measured via a sphygmomanometer and oxygen saturation levels were determined using a portable pulse oximeter (Model 9590 Oximeter, Nonin ® Medical, Inc., Plymouth, MN, USA). Dyspnea, fatigue, and leg fatigue were assessed using the Modified Borg Scale, and respiratory rate was determined by counting the number of breaths taken per minute. Patients were instructed to walk at their maximum pace without running, adhering to their comfort. It was emphasized to the patients that they could pause and rest during the test if they felt unwell; however, it was clear that any time spent resting would be included in the overall test duration. Standard phrases were used to encourage patients at each minute. As a result of the test, the total distance of the patients was calculated and reported in meters (m). For analysis, the longest walking distance between the two tests was used. The expected 6-MWT walking distance was calculated using Li et al.'s reference equation [102].

Males: 554.16 + [difference in heart rate x 1.76] + [height (cm) x 1.23] m

Females: 526.79 + [difference in heart rate x 1.66] + [height (cm) x 0.62] m

3.2.8. Maximal Exercise Capacity: Cardiopulmonary Exercise Test

The maximum exercise capacity was assessed using the Cardiopulmonary Exercise Test (CPET). Cardiopulmonary exercise testing evaluates the pulmonary, cardiovascular, and metabolic systems' integrated response. Measurements were made on a treadmill (Trackmaster®, 3017 Full Vision, Newton, Ks USA) using a metabolic cart (Cosmed, Quark CPET, Italy). Throughout the test, parameters such as heart rate (HR), oxygen saturation (SpO2), arterial blood pressure, and a 12-lead ECG (utilized for assessing rate, rhythm, and S-T segment morphology) were continuously monitored. Calibration of the device was conducted before each test.

The CPET consists of three phases: rest, loading, and recovery. Resting data was recorded in the first three minutes before starting the test. After the test, the first three minutes were warm up, and the loading phase started. Workload increments were set between 10 and 50 watts. The loading period was continued until the maximum exercise capacity was reached based on heart rate (HR), heart rate reserve (HRR), and respiratory exchange ratio (RER). The recovery period started when the patient reached maximal heart rate (HRR<10) or RER

above 1.0; after the recovery period, the test was concluded. According to the American Thoracic Society (ATS) and American College of Chest Physicians (ACCP) guidelines, if symptoms like (quadriceps muscle fatigue, chest pain, dyspnea, or fatigue) occurred, the test was finished [103].

The data collected during the rest and recovery period were: VO_2 (oxygen uptake) (ml/min), VO_2kg (oxygen uptake in kg) (ml/min/kg), O_2HR (oxygen pulse) (ml), VCO_2 (carbon dioxide output) (ml), VE (minute ventilation) (l/min), BF (breathing frequency) (breath/min), RER (respiratory exchange ratio), EqO_2 (ventilator equivalent of oxygen), $EqCO_2$ (ventilator equivalent of carbon dioxide), HR (heart rate) (rate/min), HRR (heart rate reserve) (l/min), MET (metabolic equivalent), SpO_2 (oxygen saturation) (%), systolic and diastolic blood pressure (mmHg), dyspnea (modified Borg scale), fatigue (modified Borg scale) and quadriceps fatigue (modified Borg scale). Moreover, during the loading period every 30 seconds, the data collected were: VO_2 (oxygen uptake) (ml/min), VO_2kg (oxygen uptake in kg) (ml/min/kg), VO_2% (percentage of oxygen uptake), VO_2kg% (percentage of oxygen uptake in kg), O_2HR (oxygen pulse) (ml), O_2HR% (percentage of oxygen pulse), VCO_2 (carbon dioxide output) (ml), VE (minute ventilation) (l/min), VE% (percentage of minute ventilation), EqO_2 (ventilator equivalent of oxygen), $EqCO_2$ (ventilator equivalent of carbon dioxide), HR (heart rate) (rate/min), HR%, HRR (heart rate reserve) (l/min), BF (breathing frequency) (breath/min), BR% (breathing reserve percentage), RER (respiratory exchange ratio), SpO_2, MET, and workload (w).After the end of the test, systolic and diastolic blood pressure (mmHg), dyspnea (modified Borg scale), fatigue (modified Borg scale), and leg fatigue (modified Borg scale) were recorded. The test concluded upon reaching the maximum heart rate, Respiratory Exchange Ratio (RER) of 1.0 or higher, or when symptoms such as dyspnea, chest pain, fatigue, or ST-segment elevation occurred [103].

3.2.9. Physical Activity Levels

Physical activity level was assessed using a metabolic Holter device (Sensewear®, BodyMedia®, Inc. Pittsburgh, USA). Participants wore the device for 4 days and were allowed only to remove it for 1 hour during bathing. The device was attached to the triceps brachii muscle of the non-dominant arm [104]. The following variables were computed: total energy expenditure (joule/day), Active energy expenditure (joule/day) above 3 metabolic

equivalents (MET), average MET value (MET/day), number of steps (steps/day), physical activity duration (minutes/day), time spent lying down (minutes/day), sleep duration (minutes/day) and wear time (min/day) [105]. The derived variables, together with age, gender, height, and weight information, were analyzed using the "BodyMedia® SenseWear® 7.0 Software" analysis program. The patient's physical activity levels were determined according to the step count data recorded from the device.

Physical activity level of individuals according to their step count; for girls <7000 steps/day= inactive, 7000-9499 steps/day= low active, 9500-11999 steps/day= somewhat active, 12000-14499 steps/day= active, >14500 steps/day= highly active, for boys < 10000 steps/day = inactive, 10000-12499 steps/day = low active, 12500-14999 steps/day = somewhat active, 15000-17499 steps/day = active, >17500 steps/day = highly active [106]. According to MET values, physical activity levels are <1.5 MET= inactive, 1.5-3.99 MET= low active, 4-5.99 MET= moderately active, and >6 MET= highly active [107].

3.2.10. Muscle Oxygenation

Muscle oxygenation was evaluated using the “Moxy®” monitor device (Moxy, Fortiori Design LLC, Minnesota, USA). During 6-MWT and CPET, the device was placed at the motor point of the Quadriceps muscle and secured with adhesive tape. Parameters measured included: during rest SmO_2 (SmO_2 at rest), total hemoglobin (THb), during 6-MWT and CPET minimum and maximum SmO_2 values, mean SmO_2 (SmO_{2avg}), and total hemoglobin minimum and maximum values (SmO_{2min}, SmO_{2max}, ΔSmO_2, $SmO_{2avg\text{-}min}$, $SmO_{2avg\text{-}max}$, $\Delta SmO_{2avg,}$ THb_{min}, THb_{max}, ΔTHb) also during one-minute recovery values recorded were: SmO_2, SmO_{2avg}, and THb (SmO_{2recv}, $SmO_{2recv\text{-}avg}$, THb_{recv}). The muscle oxygen saturation values are expressed as percentages (%) and THb in g/dl.

The Moxy monitor is a NIRS device that measures local oxygen saturation (SmO_2) and total hemoglobin (THb) in the muscle capillaries below its point of position. Additionally, the gadget uses four light-emitting diodes to sequentially generate light waves between 630 and 850 nm. The device detects the amount of dispersed light that returns to two detectors placed 12.5 and 25 mm from the light source after these waves pass through the underlying tissue. The devices' calculations enable the determination of THb and the percentage of SmO_2 within the monitored area [80]. Measured SmO_2 is the ratio of oxyhemoglobin to the sum of oxyhemoglobin and deoxyhemoglobin multiplied by one hundred. High effort in the muscle

causes low SmO_2 levels at the point where oxygen demand cannot be met. Other chemical and neurological factors affect the SmO_2 hemoglobin dissociation curve shift [108].

3.2.11. Quality of life

Varni et al. developed the Quality of Life Scale for Children (PedsQL) in 1999. It consists of 23 items divided into 4 subscales. There are eight elements that assess physical functioning, five that assess emotional functionality, five that assess social functionality, and five that assess functionality linked to education. In addition to the form being available for parents and kids individually, there are other scales designed for kids of varying ages. As a result, there are scales for kids ages 2-4, 5-7, 8-12, and 13-18.

For parents, separate forms are available for the age groups 2-4, 5-7, 8-12, and 13-18. Each item is scored between 0-100, where 'never' is marked as 0=100, 'rarely' as 1=75, 'sometimes' as 2=50, 'often' as 3=25, and 'almost always' as 4=0 points. The sum of the points is divided by the total number of items completed to determine the final score. Better perceived health-related quality of life is indicated by a higher PedsQL total score [87-89, 109].

3.2.12. Dyspnea (Shortness of breath)

The modified Borg Scale (mBorg scale) was used to score dyspnea. MBorg scale is a subjective scale that scores shortness of breath at rest and during activity between 0 and 10. A score of 0 represents the absence of breathlessness ("none"), while a score of 10 ("very severe") denotes the most severe level of breathlessness [110]. The shortness of breath was assessed before, after, and after a one-minute recovery period during 6-MWT and different stages of CPET.

3.3. Statistical Analysis

Statistical analysis was conducted using SPSS 27, a Windows-based program. The sample size was determined based on the present study data from a peakVO_{2kg} pilot study, with a significance level (α) of 0.05 and 80% power, requiring a minimum of 11 participants per group. The normality of the variables was assessed both visually (using histograms and probability plots) and analytically (via the Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive analyses presented the mean difference with a 95% confidence interval (95%

CI) and standard deviation for normally distributed variables, percentages (%) for countable variables, and median with minimum and maximum values for non-normally distributed variables. For normally distributed variables, an independent sample t-test (Student's t-test) was used for comparison, while the Mann-Whitney U test was employed for non-normally distributed data. Categorical data were analyzed using the Chi-square test. The significance level for statistical analysis was set at $p \leq 0.05$. The results were interpreted by conducting post-hoc power analysis using peakVO_{2kg} values.

4. FINDINGS

This study included 19 patients with PID referred for cardiopulmonary rehabilitation from Dr. Sami Ulus Hospital Pediatric Immunology and Allergy Diseases Department, to Gazi University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Cardiopulmonary Rehabilitation Unit, between May 2023 and May 2024, and 15 age- and gender-matched healthy children without diagnosed any disease. Fourteen out of nineteen patients with PID and 15 healthy subjects were analyzed and compared (Figure 4.1).

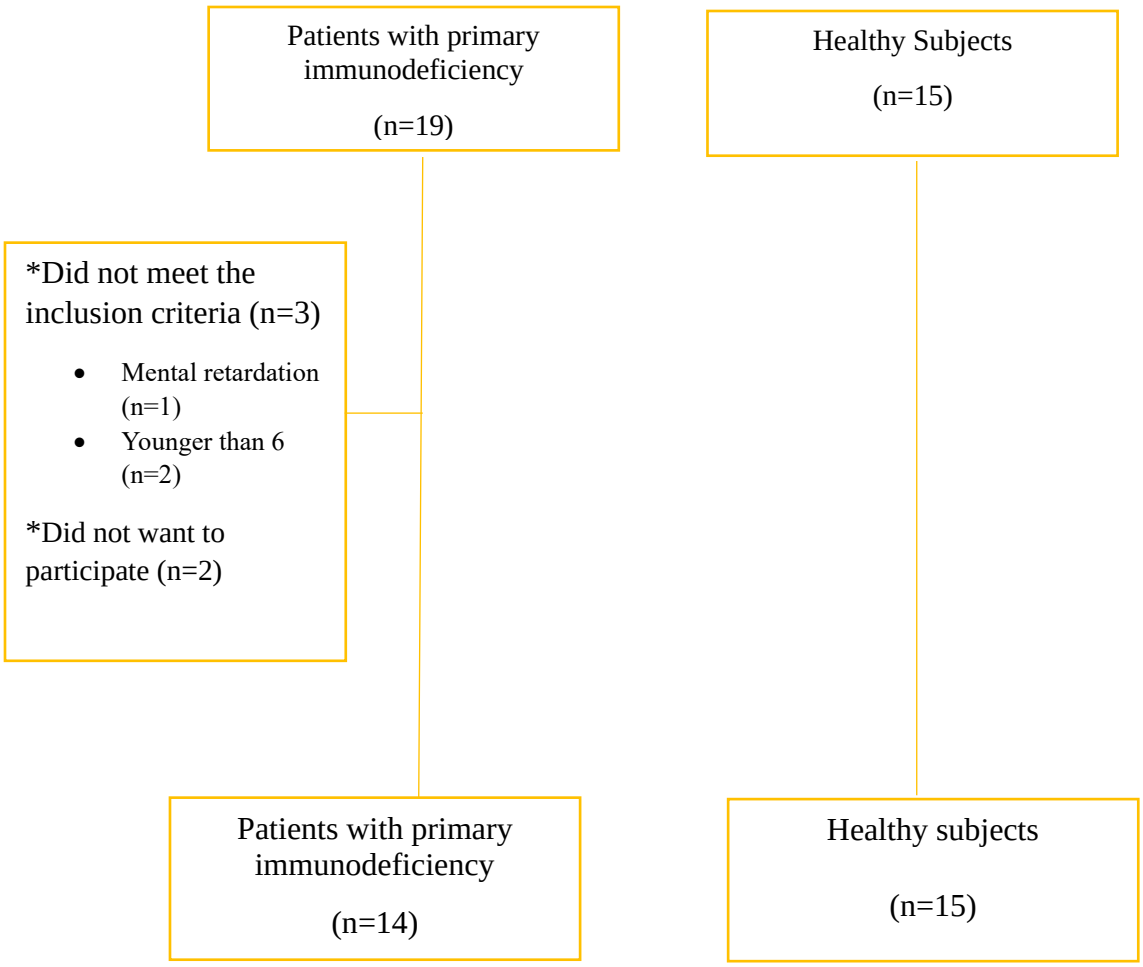

Figure 4.1. "STROBE" flowchart of patients with primary immunodeficiency and healthy subjects

The age, height, body weight, body mass index, and Z-scores of patients with primary immunodeficiency and healthy children were statistically similar ($p>0.05$, Table 4.1).

Table 4.1. Comparison of demographic characteristics of patients with primary immunodeficiency and healthy children.

Characteristics	Primary immunodeficiency X±SD/Median (IQR)	Healthy children X±SD/Median (IQR)	p
Age (years)	13.0 (9.75 - 17.25)	11.0 (9.0-14.0)	0.34
Height (cm)	151.21±14.91	149.50±16.19	0.77
Height Z score (SD)	-1.035±1.254	-0.268±1.0142	0.81
Body weight (kg)	46.21±13.63	41.57±11.91	0.33
Body weight Z score (SD)	-0.80±1.62	-0.41±0.99	0.43
Body mass index (kg/m²)	19.72±3.22	18.18±2.13	0.13
Body mass index Z score (SD)	-0.32±1.23	-0.36±0.96	0.91

Independent sample t test, Mann-Whitney U test, SD: Standard deviation, *p<0.05

The gender distributions of patients with primary immunodeficiency and healthy children were statistically similar (p>0.05, Table 4.2).

Table 4.2. Comparison of the genders between patients with primary immunodeficiency and healthy children

	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Male	12	85.7	11	73.3	0.65
Female	2	14.3	4	26.7	

Fisher's Exact chi-square test, p>0.05.

The height Z score distributions of patients with primary immunodeficiency and healthy children were statistically similar (p>0.05, Table 4.3).

Table 4.3. Comparison of the classification of patients with primary immunodeficiency and healthy control according to height Z scores.

Classification by Z score	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Severe short stature(<-3SD)	4	28.6	0	0	
Short stature (≤-3 SD-<-2 SD)	1	7.1	1	6.7	0.80
Normal stature (≥-2 SD-≤+2 SD)	9	64.3	14	93.3	
Tall stature (>+2 SD-≤+3 SD)	0	0	0	0	

Chi-square test, SD: Standard deviation, p>0.05

The weight Z score distributions of patients with primary immunodeficiency and healthy children were statistically similar (p>0.05, Table 4.4).

Table 4.4. Comparison of the classification of patients with primary immunodeficiency and healthy children according to weight Z scores.

Classification by Z score	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Severe underweight(<-3SD)	1	7.1	0	0	
Underweight (≤-3 SD-<-2 SD)	3	21.4	1	6.7	0.26
Normal (≥-2 SD)	10	71.4	14	93.3	

Chi-square test, SD: Standard deviation, p>0.05.

The body mass index Z score distributions of patients with primary immunodeficiency and healthy children were statistically similar (p>0.05, Table 4.5).

Table 4.5. Comparison of classifications of patients with primary immunodeficiency and healthy children according to body mass index Z scores.

Classification by Z score	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Severe underweight (<-3SD)	2	14.3	1	6.7	
Underweight (≤-3 SD-<-2 SD)	3	21.4	3	20.0	
Normal Weight (≥-2 SD-≤+1SD)	8	57.1	11	73.3	0.62
Overweight (<+1SD-≤+2SD)	1	7.1	0	0	
Obese (>+2SD)	0	0	0	0	

Chi-square test, SD: Standard deviation, p>0.05.

The education level between patients with primary immunodeficiency and healthy children were similar (p>0.05, Table 4.6).

Table 4.6. Comparison of education levels of patients with primary immunodeficiency and healthy children.

Education levels	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Primary school	5	35.7	5	33.3	
Middle school	3	21.4	5	33.3	0.69
High school	5	35.7	5	33.3	
Left school	1	7.1	0	0	

Chi-square test, p>0.05

There was a significant difference between patients with primary immunodeficiency and healthy children regarding consanguineous marriages. Fifty percent of the patients had a history of consanguineous marriage in the family (p<0.05, Table 4.7).

Table 4.7. History of consanguineous marriage in the families of patients with primary immunodeficiency and healthy children.

Consanguinity history	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Yes	7	50	0	0	**0.02***
No	7	50	15	100	

Chi-square test, ***p>0.05**

The distribution of patients with primary immunodeficiency according to their use of intravenous immunoglobulin G replacement therapy is given in Table 4.8.

Table 4.8. Distribution of IVIG therapy status of patients with primary immunodeficiency.

IVIG Therapy Status	Primary immunodeficiency		Dose ranges
	n	%	
IVIG	12	85.7	(15-35) g/kg
Non-IVIG	2	14.3	

IVIG: Intravenous immunoglobulin G

Time of onset of symptoms in patients with primary immunodeficiency is given in Table 9.

Table 4.9. Time of onset of symptoms in patients with primary immunodeficiency

Time of onset of symptoms	Primary immunodeficiency	
	n	%
From birth	4	28.6
1-3 (years)	6	42.85
>4 (years)	4	28.6

The medical drugs other than IVIG used by children with primary immunodeficiency is given in Table 4.10.

Table 4.10. Medical drugs other than IVIG used by children with primary immunodeficiency

Medical drugs	Primary immunodeficiency	
	n	%
Bactrim	6	42.9
Euthyrox	1	7.1
Rupafin	1	7.1
Mometix	1	7.1
Patanol	1	7.1

The distribution of genetic mutations in patients with primary immunodeficiency is given in Table 4.11.

Table 4.11. Primary immunodeficiency gene mutations.

Genetic Mutation	Primary immunodeficiency	
	n	%
BTK	3	21.4
CTLA4	2	14.4
MAGT1	1	7.1
TAPBP	1	7.1
IGLL1	1	7.1
RFX5	1	7.1
TNFRSF6	1	7.1
Unknown	4	28.7

The distribution of patients with primary immunodeficiency based on the classification of International Union of Immunological Societies categorized under Inborn Errors of Immunity is provided in Table 4.12.

Table 4.12. Primary immunodeficiency children divided by the Inborn Errors of Immunity group.

Classification	Primary immunodeficiency	
	n	%
Combined immunodeficiencies	2	14.3
Predominantly antibody deficiencies	8	57.2
Disease of immune dysregulation	3	21.4
Phenocopies of inborn error of immunity	1	7.1

The number of exacerbations and hospital visits within a previous year in patients with primary immunodeficiency is given in Table 4.13.

Table 4.13. Number of exacerbations and hospital visits in patients with primary immunodeficiency within the previous year.

	Primary immunodeficiency Median (IQR)
Number of exacerbation (<1 year) (n)	0 (0-0)
Number of hospital visits (<1 year) (n)	12 (12-12)

There was no statistical difference in exercise habits between patients with primary immunodeficiency and healthy children ($p>0.05$, Table 4.14).

Table 4.14. Comparison of exercise habits between primary immunodeficiency children and healthy children.

	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Yes/No	2/12	14.3/85.7	2/13	13.3/86.7	0.67

Chi-square test, p>0.05

The signs and symptoms of patients with primary immunodeficiency is given in Table 4.15.

Table 4.15. Signs and symptoms of children with primary immunodeficiency

Signs and symptoms	Primary immunodeficiency	
	n	%
Cough (Yes/No)	5/9	35.7/64.3
• **Productive**	2	40.0
• **Nonproductive**	3	60
Dyspnea at rest (Yes/No)	1/13	7.1/92.9
Dyspnea with effort (Yes/No)	7/7	50.0/50.0
Orthopnea (Yes/No)	0	0
Sputum (Yes/No)	6/8	42.9/57.1
• **Mucoid**	6	100
• **Purulent**	0	0
• **Mucopurulent**	0	0
Weight loss (Yes/No)	1/13	7.1/92.9
Problems while eating (Yes/No)	0	0
Night sweats (Yes/No)	5/9	35.7/64.3
Hemoptysis	0	0

Comparison of exertional dyspnea perceptions of patients with primary immunodeficiency and healthy children according to the modified Borg scale is given in Table 4.16. The exertion dyspnea perceptions of children with primary immunodeficiency were statistically significantly higher than those of healthy children (p<0.05).

Table 4.16. Comparison of exertional dyspnea between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	Healthy children	p
	Median (IQR)	Median (IQR)	
Exertional dyspnea (M. Borg 0-10)	1 (0-3)	0 (0-0)	**0.02***

Mann-Whitney U test, ***p<0.05**

The comparison of pulmonary function test parameters between patients with primary immunodeficiency and healthy children is given in Table 4.17. The patients' FEV_1/FVC was

statistically significantly decreased when compared with healthy children ($p<0.05$). The FVC (L), FVC (%), FEV_1 (L), FEV_1 (%), PEF (L), PEF (%), $FEF_{25-75\%}$ (L), $FEF_{25-75\%}$ (%) parameters of the groups were statistically similar ($p>0.05$). Four of the patients (28.57%) had obstructive, two (14.29%) had mixed and one (7.17%) had restrictive type pulmonary function abnormalities.

Table 4.17. Comparison of pulmonary function test between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	**Healthy children**	**Mean diff. 95%CI/U**	**p**
	X±SD/Median (IQR)	**X±SD/Median (IQR)**		
FVC (L)	3.1629±1.050	3.030±0.963	0.132 [(-0.63)-0.89]	0.72
FVC (%)	98.20 (88-110)	106.10 (89-109.50)	100	0.82
FEV_1 (L)	2.55(1.99-3.14)	2.63 (1.95-2.90)	102	0.89
FEV_1 (%)	97.25 (86.40-106.0)	102.24 (94-108.20)	84.50	0.37
FEV_1/FVC	87.16 (82.0-89.0)	89.04 (87.70-94.88)	58.50	**0.04***
PEF (L)	4.54 (3.22-5.85)	5.0 (4.40-5.69)	85.0	0.38
PEF (%)	84.90 (74.0-93.0)	89.50 (85.0-95.80)	71	0.13
$FEF_{25-75\%}$ (L)	2.63 (2.10-4.16)	95.80 (2.72-2.03)	98.50	0.77
$FEF_{25-75\%}$ (%)	98.10±23.68	97.17±19.21	0.93 [(-15.4)-17.31	0.90

Mann-Whitney U test, Independent student t test, FVC: Forced Vital Capacity, FEV_1: forced expiratory volume in 1 second, FEV_1/FVC: forced expiratory volume in 1 second and forced vital capacity ratio, PEF: peak expiratory flow, $FEF_{25-75\%}$: forced expiratory flow at 25-75% of the pulmonary volume, ***p<0.05.**

Respiratory muscle strength values of patients with primary immunodeficiency and healthy children are given in Table 4.18. The MEP (%) value of the patients was statistically significantly decreased when compared with the healthy children ($p<0.05$). The MIP, MIP (%), MEP values were statistically similar in the groups ($p>0.05$). Six (42.86%) patients had decreased MIP, and three (21.43%) had MEP than the 80% of expected.

Table 4.18. Comparison of respiratory muscle strength between children with primary immunodeficiency and healthy children

	Primary immunodeficiency X±SD/Median (IQR)	**Healthy children X±SD/Median (IQR)**	**Mean diff. 95%CI/U**	**p**
MIP (cmH_2O)	80.92±36.28	98.26±21.44	-17.33 [(-39.86)-5.18]	0.12
MIP (%)	86.15±39.55	111.46±29.54	-25.28 [(-51.75)-1.19]	0.60
MEP (cmH_2O)	106.07±38.99	125.66±27.48	-19.59 [(-45.15)-5.96]	0.12
MEP (%)	83.89±31.66	113.96±38.31	-30.07 [(-56.96)-(-3.18)]	**0.03***

Independent student t test, MIP: Maximal inspiratory pressure, MEP: Maximal expiratory pressure, ***p<0.05.**

Comparison of respiratory muscle endurance parameters of patients with primary immunodeficiency and healthy children is given in Table 4.19. Respiratory muscle endurance (cmH_2O), (%), SpO_2 (rest) (%), dyspnea (rest), ΔSpO_2 (%) and ΔDyspnea values were statistically similar in the groups ($p>0.05$). Nine (64.28%) patients had decreased respiratory muscle endurance pressure than the 80% expected.

Table 4.19. Comparison of respiratory muscle endurance between children with primary immunodeficiency and healthy children.

	Primary immunodeficiency X±SD/Median (IQR)	**Healthy children X±SD/Median (IQR**	**Mean diff. 95%CI/U**	**p**
Respiratory muscle endurance (cmH_2O)	25.70 (18.60-59.20)	52.0 (34.0-68.40)	64.0	0.13
Respiratory muscle endurance (%)	68.26 (57.14-103.34)	83.41 (68.10-108.90)	77.0	0.45
Endurance time (s)	299.92±167.25	346.05±128.92	-46.12 [(-159.44)-67.19	0.41
SpO_2 (rest) (%)	98(97-98)	97 (97-98)	89.0	0.07
Dyspnea (rest) M. Borg (0-10)	0 (0-0)	0 (0-0)	90.0	0.22
ΔSpO_2 (%)	-0.5 [(-1)-2]	1 (0-2)	73.50	0.16
ΔDyspnea (M. Borg) (0-10)	1.25 (0-3)	1 (0-3)	83.0	0.32

Mann-Whitney U test, Independent student t test; $p<0.05$.

Comparison of peripheral muscle strength between patients with primary immunodeficiency and healthy children is given in Table 4.20. Right knee extensors (%) and right shoulder abductors (%) muscle strength of patients with primary immunodeficiency were statistically significantly decreased when compared to healthy children ($p<0.05$). Right knee extensors (N) and right shoulder abductors (N) muscle strength were statistically similar in the groups ($p>0.05$).The right knee extensor muscle strength of nine patients (64.28%), left knee extensor muscle strength of eight patients (57.14%), right shoulder abductor muscle strength of eight patients (57.14%), and left shoulder abductor muscle strength of ten patients (71.42%) were all below the 80% of expected.

Table 4.20. Comparison of peripheral muscle strength between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency X±SD/Median (IQR)	Healthy children X±SD/Median (IQR)	Mean diff. 95%CI/U	p
Knee extensors (right)(N)	211.59±70.46	244.54±73.80	-32.95[(-88.0)-22.11]	0.23
Knee extensors % (right)(N)	75.08±20.87	90.78±19.05	-15.70[(-30.91)-(-0.48)]	**0.04***
Knee extensors (left)(N)	231.22±73.33	276.52±103.70	-44.30[(-112.61)-24.0	0.19
Knee extensors% (left) (N)	85.67±35.51	101.52±27.84	-15.84[(-40.06)-8.37]	0.19
Shoulder abductors (right)(N)	111.50 (96.0-12.60)	125.0(90.0-147.0)	78.50	0.24
Shoulder abductors % (right)(N)	74.25±25.11	97.26±28.83	-23.0[(-43.67)-(-2.43)]	**0.03***
Shoulder abductors (left) (N)	105.80 (72.60-120.0)	121.0 (85.0-136.0)	82.0	0.31
Shoulder abductors % (left)(N)	65.29 (50.22-88.0)	78.73 (72.20-100.81)	53.0	**0.02***

Mann-Whitney U test, Independent student t test; N: Newton, ***p<0.05.**

The comparison of 6-MWT findings of patients with primary immunodeficiency and healthy children is given in Table 4.21. Six-MWT distance of the patients was statistically significantly shorter when compared with the healthy children ($p<0.05$). All of the patients (100%) and six (40%) of the healthy children had lower 6MWD than the 80% expected.

The ΔHR, HRmax, HR max (%), SBP (rest), Δ SBP, BF (rest), and Δ BF parameters were all statistically significantly decreased in patients with primary immunodeficiency compared to healthy children ($p<0.05$). Patients with primary immunodeficiency had lower maximal heart rate and expected percentage, higher systolic blood pressure and higher breathing frequency compared to the healthy children. HR (rest), SpO_2 (rest), ΔspO_2, DBP (rest), ΔDBP, Dyspnea (rest), ΔDyspnea, Fatigue (rest), ΔFatigue, QF fatigue (rest), ΔQF fatigue parameters were statistically similar between the groups ($p>0.05$).

Table 4.21. Comparison of 6-MWT and vital sign responses during of patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	Healthy children	Mean diff. 95%CI/U	p
	X±SD/Median (IQR)	X±SD/Median (IQR)		
HR (rest) (beats/min)	80.07±12.71	84.53±12.79	-4.46 [(-14.18)-5.26]	0.35
ΔHR (beats/min)	46.85±14.05	63.66±23.69	-16.80 [(-31.66)-(-1.82)]	**0.02***
HRmax (beats/min)	126.92±20.89	148.20±17.89	-21.27[(-36.06)-(-6.47)]	**0.006***
HR max (%)	61.33±9.97	71.31±9.40	-9.97 [(-17.35)-(-2.58)]	**0.01***
SpO_2 (rest) (%)	98 (97-98)	98 (97-98)	91	0.96
Δ SpO_2 (%)	-0.42±1.28	-0.20±1.08	-0.22 [(-1.13)-0.67]	0.60
SBP (rest) (mmHg)	110 (110-120)	100 (110-130)	45.50	**0.004***
Δ SBP (mmHg)	15 (10-20)	20 (20-30)	50	**0.01***
DBP (rest) (mmHg)	72.5 (70-80)	70 (60-80)	88	0.44
Δ DBP (mmHg)	10 (10-10)	10 (0-20)	90	0.48
BF (rest) (breath/min)	20 (20-24)	20 (20-20)	60	**0.01***
Δ BF (breath/min)	8 (4-8)	12 (8-16)	49.5	**0.01***
Dyspnea (rest) (M. Borg) (0-10)	0 (0-0)	0 (0-0)	82.50	0.06
Δ Dyspnea (M. Borg) (0-10)	0 (0-0.5)	1 (0-2)	84.50	0.34
Fatigue (rest) (M. Borg) (0-10)	0 (0-0)	0 (0-0)	102	0.85
Δ Fatigue (M. Borg) (0-10)	0.75 (0-2)	0.5 (0-2)	101.5	0.87
QF fatigue (rest) (M. Borg) (0-10)	0 (0-0)	0 (0-0)	104.5	0.96
Δ QF fatigue (M. Borg) (0-10)	0.5 (0-3)	0.5 (0-3)	98	0.74
6-MWT distance (m)	543 (535.2-572.4)	600 (540-702.6)	60	**0.04***
6-MWT distance (%)	66.75 (65.50-70.96)	77.70 (65.48-84.33)	61	**0.05***

Mann-Whitney U test, Independent student t test; HR: Heart rate, SpO_2: oxygen saturation, SBP: systolic blood pressure, DBP: diastolic blood pressure, BF: breathing frequency, QF: quadriceps femoris, M.Borg: modified Borg scale, Δ SpO_2: oxygen saturation difference, ΔHR: heart rate difference, Δ SBP: systolic blood pressure difference, Δ DBP: diastolic blood pressure difference, Δ Dyspnea: dyspnea difference, Δ Fatigue: fatigue perception difference, Δ QF fatigue: quadriceps femoris fatigue difference, ***p<0.05**

The comparison of resting cardiopulmonary exercise test values of patients with primary immunodeficiency and healthy children are given in Table 4.22. The RER, VO_{2kg}, HRR values in patients were lower and $EqCO_2$ higher compared to healthy children with statistically significant difference ($p<0.05$). Whereas, VO_2, MET, HR, O_2HR, VCO_2, BF, EqO_2, SBP, DBP, dyspnea, fatigue, QF fatigue and SpO_2 values were statistically similar in groups ($p>0.05$).

Table 4.22. Comparison of resting cardiopulmonary exercise test values of patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	Healthy children	Mean diff. 95%CI/U	p
	X±SD/Median (IQR)	X±SD/Median (IQR)		
RER	0.77 (0.73-0.79)	0.82 (0.79-86)	49	**0.01***
VO_2 (ml/min)	325.47±86.52	346.62±77.28	-21.15 [(-83.56)-41.26]	0.49
VO_{2kg} (ml/min/kg)	6.99±1.118	8.34±1.93	-1.34[(-2.56)-(-0.12)]	**0.03***
MET	2.0±0.37	2.3±0.57	-0.27 [(-0.65)-0.09]	0.14
VE (l/min)	10.84±2.23	11.98±2.56	-1.14 [(-2.98)-0.68]	0.21
HR (beat/min)	100.7±2.23	102.99±13.05	-2.23 [(-11.45)-6.99]	0.62
HRR (beat/min)	91.25 (71-91.5)	98 (77-113)	61.5	**0.05***
O_2HR (ml/beat)	3.08±0.65	3.24±0.82	-0.16 [(-0.73)-0.40]	0.56
VCO_2 (ml/min)	275.78±103.92	291.18±65.06	-15.39 [(-80.96)-52.0]	0.63
BF (breath/min)	20.6±3.2	21.9±3.5	-1.26 [(-3.87)-1.33]	0.32
EqO_2	29.69±4.63	29.35±3.97	0.34 [(-2.96)-3.62]	0.83
$EqCO_2$	37.50±3.53	34.46±3.79	3.04 (0.24-5.84)	**0.03***
SBP (mmHg)	117.27 (110-130)	113.10 (110-120)	86.50	0.40
DBP (mmHg)	80 (70-84.5)	80 (70-90)	96	0.68
Dyspnea (M. Borg) (0-10)	0 (0-0)	0 (0-0)	63	0.10
Fatigue (M. Borg) (0-10)	0 (0-0)	0 (0-0)	77	1.0
QF fatigue (M. Borg) (0-10)	0 (0-0)	0 (0-0)	77	1.0
SpO_2 (%)	99.13 (99-100)	99 (99-100)	89	0.46

Mann-Whitney U test, Independent student t test, RER: respiratory exchange ratio, VO_2: oxygen uptake, VO_{2kg}: oxygen uptake per kilogram, MET: metabolic equivalent, VE: minute ventilation, HR: heart rate, HRR: heart rate reserve, O_2HR: oxygen pulse, VCO_2: carbon dioxide output, BF: breathing frequency, EqO_2: ventilator equivalent of oxygen, $EqCO_2$: ventilator equivalent of carbon dioxide, SBP: systolic blood pressure, DBP: diastolic blood pressure, QF Fatigue: quadriceps femoris muscle fatigue, SpO_2: oxygen saturation, ***p<0.05.**

The comparison of anaerobic threshold cardiopulmonary exercise test values in between patients with primary immunodeficiency and healthy children is give in Table 4.23. The RER, VO_{2kg} and VE values in patients were lower and $EqCO_2$ higher compared to healthy children with statistically significant difference ($p<0.05$). The VO_2, MET, HR, HRR, O_2HR, VCO_2, BF, EqO_2, SBP, DBP, dyspnea, fatigue, QF fatigue, SpO_2 and work load values were statistically similar in groups ($p>0.05$).

Table 4.23. Comparison of anaerobic threshold cardiopulmonary exercise test values of patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	Healthy children	Mean diff. 95%CI/U	
	X±SD/Median (IQR)	X±SD/Median (IQR)		p
RER	0.83±0.09	0.94±0.11	-0.11 [(-0.19)-(-0.03)]	**0.008***
VO_2 (ml/min)	1178.50 (941-1330.25)	1442 (857-2239)	67	0.09
VO_{2kg} (ml/min/kg)	25.69±6.85	34.51±12.64	-8.81 [(-16.65)-(-0.98)]	**0.02***
MET	8.29±2.90	9.92±3.56	-1.62 [(-4.11)-0.86	0.19
VE (l/min)	36.31±8.96	49.59±22.85	-13.27 [(-26.69)-0.14]	**0.05***
HR (beats/min)	157.80±17.23	169.45±23.23	-11.64 [(-27.32)-4.03]	0.13
HRR (beats/min)	32.96±18.34	32.79±20.70	0.17 [(-14.77)-15.12]	0.98
O_2HR (ml/beat)	7.20 (6.40-7.89)	7.70 (5.10-77.80)	79	0.25
VCO_2 (ml/min)	1007.50 (742-1252)	1439 (708-2300)	63	0.06
BF (breath/min)	37.59±12.96	40±11.07	-2.41 [(-11.58)-6.74]	0.59
EqO_2	29.19±4.39	29.69±3.10	-0.49 [(-3.38)-2.38]	0.72
$EqCO_2$	35.95±5.39	32.13±2.73	3.82 (0.59-7.04)	**0.02***
SpO_2 (%)	97.79 (97-99)	98 (98-100)	67.5	0.09
Work load (W)	125.50 (92.10-176)	113.49 (106.3-178.47)	91	0.54

Mann-Whitney U test, Independent student t test, RER: respiratory exchange ratio, VO_2: oxygen uptake, VO_{2kg}: oxygen uptake per kilogram, MET: metabolic equivalent, VE: minute ventilation, HR: heart rate, HRR: heart rate reserve, O_2HR: oxygen pulse, VCO_2: carbon dioxide output, BF: breathing frequency, EqO_2: ventilator equivalent of oxygen, $EqCO_2$: ventilator equivalent of carbon dioxide, SBP: systolic blood pressure, DBP: diastolic blood pressure, QF Fatigue: quadriceps femoris muscle fatigue, SpO_2: oxygen saturation, Work load (W: watt), ***p<0.05.**

The comparison of peak cardiopulmonary exercise test values between patients with primary immunodeficiency and healthy children is given in Table 4.24. VO_{2kg}, MET, HR, and SpO_2 values in patients were lower $EqCO_2$, Dyspnea, Fatigue, and QF fatigue were higher compared to healthy children with statistically significant difference ($p<0.05$). The RER, VO_2, VO_2%, VO_{2kg}, VO_{2kg}%, VE, VE%, HR%, HRR, O_2HR, O_2HR%, VCO_2, BF, EqO_2, SBP, DBP, and workload were statistically similar in the groups ($p>0.05$). Six (42.85%) patients and three (20%) healthy children had lower peak VO_{2kg}, than 80% expected. Thirteen (93%) patients and fifteen (100%) healthy children reached a maximal heart rate. One patient (7%) finished due to leg fatigue (M. Borg scale (9 points)) and dyspnea (M. Borg scale (6 points)). There were no noted ST-segment elevations in any of the patients or healthy children during the tests.

Table 4.24. Comparison of peak cardiopulmonary exercise test values of patients with primary immunodeficiency and healthy children

	Primary immunodeficiency	Healthy children	Mean diff. 95%CI/U	p
	X±SD/Median (IQR)	X±SD/Median (IQR)		
RER	0.98±0.13	1.05±0.06	-0.06 [(-0.14)-0.01]	0.10
VO_2 (ml/min)	1585.29 (1128-1653.58)	1648 (1416-2249)	76.5	0.21
VO_2%	81.65 (74-82.29)	82.29 (79-95)	72.50	0.15
VO_{2kg} (ml/min/kg)	33.27±5.98	42.36±6.95	-9.08 [(-14.04)-(-4.12)]	**0.001***
VO_{2kg}%	81.65 (74-82.29)	82.29 (79-95)	75.50	0.15
VCO_2 (ml/min)	1582.26 (1221-1714)	1714 (1398-2320)	77	0.22
MET	10 (9.20-11.79)	11.79 (10.70-12.80)	57.50	**0.03***
VE (l/min)	59.28 (47-59.55)	58 (50.30-87.20)	93	0.60
VE%	80.46 (73-85)	80.46 (80.46-80.46)	85.5	0.35
HR (beat/min)	183.52±7.12	190.40±5.71	-6.88 [(-11.78)-(-1.97)]	**0.008***
HR%	97.29 (95-98)	96 (91-99)	91	0.54
HRR (beat/min)	8.70±10.90	12.09±10.44	-3.39 [(-11.53)-4.74]	0.39
O_2HR (ml/beat)	8.75 (6.70-8.91)	8.70(7.70-11.60)	82	0.31
O_2HR%	86.11±12.30	85.24±12.50	0.87 [{-8.58)-10.33]	0.85
BF (breath/min)	45.91±10.15	48.64±8.89	-2.73 [(-9.99)-4.52]	0.44
EqO_2	35.25±4.07	34.18±3.65	1.07-[(-1.86)-4.02]	0.46
$EqCO_2$	37.52±5.89	33.48±4.78	4.04 [(-0.03)-8.11]	**0.05***
SBP (mmHg)	150 (146.97-153.20)	150.07 (150-160)	79.5	0.25
DBP (mmHg)	92.66 (90-100)	90 (85-100)	95	0.65
Dyspnea (M. Borg) (0-10)	3 (2-4)	1 (0-3)	34	**0.01***
Fatigue (M. Borg) (0-10)	2 (1-4)	0.75 (0-2)	42	**0.05***
QF fatigue (M. Borg) (0-10)	3 (1-3)	0.5 (0-2)	36	**0.02***
SpO_2 (%)	96.33(89-97)	98 (98-99)	38.5	**0.003***
Work load (W)	205(160-235)	155(117.21-195)	64	0.07
BR%	35.63±10.19	34.18±8.56	1.44 [(-5.77)-8.60]	0.75

Mann-Whitney U test, Independent student t test, RER: respiratory exchange ratio, VO_2: oxygen uptake, VO_{2kg}: oxygen uptake per kilogram, MET: metabolic equivalent, VE: minute ventilation, HR: heart rate, HRR: heart rate reserve, O_2HR: oxygen pulse, VCO_2: carbon dioxide output, BF: breathing frequency, EqO_2: ventilator equivalent of oxygen, $EqCO_2$: ventilator equivalent of carbon dioxide, SBP: systolic blood pressure, DBP: diastolic blood pressure, QF Fatigue: quadriceps femoris muscle fatigue, SpO_2: oxygen saturation, BR: breathing reserve, Work load (W: watt), ***p<0.05.**

The comparison of physical activity parameters between patients with primary immunodeficiency and healthy children is given in Table 4.25. Active energy expenditure, number of steps and average MET values were statistically significantly decreased in patients compared to healthy children ($p<0.05$). Whereas, total energy expenditure, physical activity and lying down durations were statistically similar in the groups ($p>0.05$).

Table 4.25. Comparison of physical activity parameters between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency X±SD/Median (IQR)	**Healthy children X±SD/Median (IQR)**	**Mean diff. 95%CI/U**	**p**
Total energy expenditure (joules/day)	7719.50 (6654-8938.01)	8656.61 (7883-11319)	74	0.17
Physical activity duration (>3 MET) (min/day)	143.50 (78-294)	226.74 (141-362)	67	0.09
Lying down duration (mins/day)	528.50 (493.75-556)	462 (378-517)	62.5	0.06
Active energy expenditure (joules/day)	1664(956-2970)	3019 (1656-6674)	60	**0.04***
Number of steps (steps/day)	9780.73 (6863-11657)	13859 (9645-15721)	46	**0.01***
Sleep duration (mins/day)	434.46±57.46	368.00±101.23	66.45 (3.65-129.25)	**0.03***
Average METs (METs/day)	1.65 (1.50-1.90)	2 (1.6-2.1)	50	**0.01***

Mann-Whitney U test, Independent student t test, MET: metabolic equivalent, ***p<0.05**

The comparison of physical activity level based on daily number of steps between patients with primary immunodeficiency and healthy children is give in Table 4.26. Physical activity level classifications of the groups according to the daily number of steps were statistically different the majority of patients had less step count ($p<0.05$). Eight (57.1%) patients and two (13.3%) of healthy children were inactive, one (7.15%) patient and three (20%) healthy children were highly active.

Table 4.26. Comparison of physical activity level based on daily number of steps between children with primary immunodeficiency and healthy children.

	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Inactive					
• **For girls: <7000 steps/day**	8	57.1	2	13.3	
• **For boys: < 10000 steps/day**					
Low active					
• **For girls: 7000-9499 steps/day**	4	28.7	2	13.4	
• **For boys: 10000-12499 steps/day**					
Somewhat active					
• **For girls: 9500-11999 steps/day**	1	7.1	5	33.3	**0.02***
• **For boys: 12500-14999 steps/day**					
Active					
• **For girls: 12000-14499 steps/day**	0	0	3	20	
• **For boys: 15000-17499 steps/day**					
Highly active					
• **For girls: >14500 steps/day**	1	7.1	3	20	
• **For boys: >17500 steps/day**					

Chi-square test, ***p>0.05**

The comparison of physical activity level classification according to average MET values of patients with primary immunodeficiency and healthy children is given in Table 4.27. There was no statistical difference between groups (p>0.05). All children low active according to their average MET values.

Table 4.27. Comparison of physical activity level classification of patients with primary immunodeficiency and healthy children according to average MET values.

	Primary immunodeficiency		Healthy children		p
	n	%	n	%	
Inactive (<1.5 MET)	0	0	0	0	
Low active (1.6–2.9 MET)	14	100	15	100	1.0
Moderately active (4-5.99 MET)	0	0	0	0	
Highly active (>6 MET)	0	0	0	0	

Chi-square test, MET: metabolic equivalent, p>0.05

The comparison of quadriceps femoris muscle oxygenation during the 6-MWT between patients with primary immunodeficiency and healthy children is given in Table 4.28. The SmO_{2max}, ΔSmO_2, $SmO_{2avg\text{-}max}$, and ΔSmO_{2avg} values were statistically significantly decreased in patients with primary immunodeficiency compared to healthy children. The SmO_{2rest}, SmO_{2min}, $SmO_{2avg\text{-}min}$, $SmO_{2recovery}$, $SmO_{2recovery\text{-}avg}$, THb_{rest}, THb_{min}, THb_{max}, ΔTHb, and $THb_{recovery}$ values were statistically similar in the groups ($p>0.05$).

Table 4.28. Comparison of quadriceps femoris muscle oxygenation during the 6-MWT between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	**Healthy children**	**Mean diff. 95%CI/U**	**p**
	X±SD/Median (IQR)	**X±SD/Median (IQR**		
SmO_{2rest} (%)	50.85±16.50	60.33±13.16	-9.47 [(-20.81)-1.85]	0.09
SmO_{2min} (%)	40.92±19.90	45.0±9.13	-4.07 [(15.73)-7.59]	0.48
SmO_{2max} (%)	55.0±16.93	65.6±11.19	-10.6 [(-21.53)-0.19]	**0.05***
ΔSmO_2 (%)	11.5 (8-20)	17 (15-23)	56	**0.03***
$SmO_{2avg\text{-}min}$ (%)	41.71±19.87	45.86±8.91	-4.15 [(-15.75)-7.44]	0.46
$SmO_{2avg\text{-}max}$ (%)	54.35±17.19	65.0±11.14	-10.64 [(-21.6)-0.32]	**0.05***
ΔSmO_{2avg} (%)	12.64±7.13	19.13±8.70	-6.49 [(-12.58)-(-0.39)]	**0.03***
$SmO_{2recovery}$ (%)	53.85±16.37	62.53±15.79	-8.67 [(-20.93)-3.58]	0.15
$SmO_{2recovery\text{-}avg}$ (%)	53.35±16.24	62.13±15.95	-8.77 [(-21.05)-3.50]	0.15
THb_{rest} (g/dl)	12.08±0.33	12.12±0.35	-0.04 [(-0.30)-0.21]	0.74
THb_{min} (g/dl)	11.97 (11.59-12.11)	11.92 (11.68-12.14)	104	0.96
THb_{max} (g/dl)	12.14±0.28	12.18±0.33	-0.03 [(-0.27)-0.2]	0.74
ΔTHb (g/dl)	0.21 (0.19-0.30)	0.20 (0.15-0.26)	86.5	0.41
$THb_{recovery}$ (g/dl)	11.98±0.27	12.10±0.33	-0.11 [(-0.34)-0.12]	0.32

Mann-Whitney U test, Independent student t test, SmO_2: local oxygen saturation, SmO_{2rest}: resting local oxygen saturation, SmO_{2min}: minimum muscle oxygenation during test, SmO_{2max}: maximum muscle oxygenation during test, $SmO_{2avg\text{-}min}$: minimum average muscle oxygen saturation during the test, $SmO_{2avg\text{-}max}$: maximum average muscle oxygen saturation during the test, $SmO_{2recovery}$: recovery muscle oxygen saturation, $SmO_{2recovery\text{-}avg}$: average muscle oxygen saturation recovery, THb_{rest}: resting total hemoglobin level, THb_{min}: minimum total hemoglobin level during test, THb_{max}: maximum total hemoglobin level during test, $THb_{recovery}$: total hemoglobin level recovery, ***p<0.05**.

The comparison of quadriceps femoris muscle oxygenation during cardiopulmonary exercise test in patients with primary immunodeficiency and healthy children is given in Table 4.29. The SmO_{2rest}, SmO_{2max}, $SmO_{2avg\text{-}max}$, and $SmO_{2recovery\text{-}avg}$, ΔTHb values were statistically significantly decreased in patients with PID compared to healthy children ($p<0.05$). The SmO_{2min}, ΔSmO_2, $SmO_{2avg\text{-}min}$, ΔSmO_{2avg}, $SmO_{2recovery}$, THb_{rest}, THb_{min}, THb_{max}, ΔTHb, and $THb_{recovery}$ values were statistically similar in groups ($p>0.05$).

Table 4.29. Comparison of quadriceps muscle oxygenation during cardiopulmonary exercise test in primary immunodeficiency and healthy children.

	Primary immunodeficiency	Healthy children	Mean Diff. 95% CI/U	p
	X±SD/Median (IQR)	X±SD/Median (IQR)		
SmO_{2rest} (%)	49.66±8.41	60.82±15.39	-11.16[(-20.71)-(-1.60)]	**0.02***
SmO_{2min} (%)	31.75±8.05	38.68±13.22	-6.93 [(-15.35)-1.40]	0.10
SmO_{2max} (%)	50.90±12.30	63.42±14.56	-12.52[(-22.83)-(-2.21)]	**0.01***
ΔSmO_2 (%)	19.15±8.06	24.73±9.26	-5.58[(-12.22)-1.05]	0.09
$SmO_{2avg-min}$ (%)	32.02±8.18	40.21±13.43	-8.18 [(-16.744)-0.36]	0.06
$SmO_{2avg-max}$ (%)	50.21±11.83	63.19±14.80	-12.98 [(-23.223)-(-2.72)]	**0.01***
ΔSmO_{2avg} (%)	18.18±8.21	22.97±8.81	-4.79[(-11.29)-1.71]	0.14
$SmO_{2recovery}$ (%)	46.46±8.56	54.09±12.97	-7.62 [(-16.07)-0.81]	0.07
$SmO_{2recovery-avg}$ (%)	45.69±8.40	53.99±12.72	-8.30 [(-16.58)-(-0.02)]	**0.04***
THb_{rest} (g/dl)	12.18±0.28	12.17±0.46	0.007[(-0.29)-0.30]	0.95
THb_{min} (g/dl)	12.0±0.19	11.89±0.38	0.11[(-0.12)-0.34]	0.33
Thb_{max} (g/dl)	12.40±0.29	12.35±0.44	0.04[(-0.24)-0.33]	0.73
ΔTHb (g/dl)	0.39±0.26	0.46±0.22	-0.06[(-0.2)-0.12]	0.48
$THb_{recovery}$ (g/dl)	12.10±0.16	12.03±0.35	0.07[(-0.14)-0.28]	0.49

Mann-Whitney U test, Independent student t test, SmO_2: local oxygen saturation, SmO_{2rest}: resting local oxygen saturation, SmO_{2min}: minimum muscle oxygenation during test, SmO_{2max}: maximum muscle oxygenation during test, $SmO_{2avg-min}$: minimum average muscle oxygen saturation during the test, $SmO_{2avg-max}$: maximum average muscle oxygen saturation during the test, $SmO_{2recovery}$: recovery muscle oxygen saturation, $SmO_{2recovery-avg}$: average muscle oxygen saturation recovery, THb_{rest}: resting total hemoglobin level, THb_{min}: minimum total hemoglobin level during test, THb_{max}: maximum total hemoglobin level during test, $THb_{recovery}$: total hemoglobin level recovery, ***p<0.05**.

The comparison of child-reported PedsQL questionnaire between patients with primary immunodeficiency and healthy children is given in Table 4.30. Psychosocial health, physical health dimensions, and total scores of the questionnaire in patients were lower compared to healthy children and were statistically significantly different ($p<0.05$).

Table 4.30. Comparison of child reported PEDs quality of life questionnaire between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	Healthy children	Mean diff. 95%CI/U	p
	X±SD/Median (IQR)	X±SD/Median (IQR)		
Psychosocial health summary score (0-100)	80.83 (70-86.66)	91.66 (78.33-98.33)	54.50	**0.02***
Physical health summary score (0-100)	79.69 (65.62-90.62)	93.75 (87.50-100)	47	**0.01***
Total score (0-100)	79.35 (71.73-86.95)	92.39(81.52-97.82)	49	**0.01***

Mann-Whitney U test, ***p<0.05.**

The comparison of parent-reported PedsQL questionnaire between patients with primary immunodeficiency and healthy children is given in Table 4.31. Parent reported psychosocial health summary score, physical health summary score and total score in patients with primary immunodeficiency compared to healthy children were statistically significantly lower ($p<0.05$).

Table 4.31. Comparison of parent reported PEDs quality of life questionnaire between patients with primary immunodeficiency and healthy children.

	Primary immunodeficiency	**Healthy children**	**Mean diff. 95%CI/U**	**P**
	X±SD/Median (IQR)	**X±SD/Median (IQR)**		
Psychosocial health summary score (0-100)	77.50 (68.33-81.66)	96.66 (90-98.33)	17	**<0.001***
Physical health summary score (0-100)	71.87 (65.62-93.75)	96.87 (93.75-100)	26	**<0.001***
Total score (0-100)	74.46 (68.47-84.78)	96.73 (90-97.82)	12.5	**<0.001***

Mann-Whitney U test, ***p<0.05.**

5. DISCUSSION

The present study revealed several key findings: patients with PID have impaired functional and maximal exercise capacity, decreased physical activity levels and quality of life, upper and lower extremity muscle weakness, and reduced muscle oxygenation during submaximal and maximal exercise tests with normal pulmonary function, respiratory muscle strength and endurance.

Patients with PID experience increased susceptibility to infections, particularly those affecting the respiratory tract. These recurrent infections can trigger chronic inflammation and structural changes within the airways. This ongoing inflammatory state often leads to lung complications, with bronchiectasis being the most common. Bronchiectasis is characterized by chronic airway inflammation, structural changes, and airflow obstruction as measured by lung function tests. Notably, mortality rates in patients with PID are known to increase with a decline in lung function [55, 111, 112]. The key finding of this study aligns with existing knowledge. The FEV_1/FVC was significantly decreased in PID patients, indicating a prevalent issue of airflow obstruction in this patient population. Half of the patients in the study exhibited impaired lung function, with 28.57% displaying an obstructive defect, 14.29% showing a mixed pattern, and 7.17% demonstrating a restrictive pattern. Previous research has primarily focused on assessing pulmonary function in adult patients with PID [56, 57, 111]. However, Che-Chiu et al. conducted a study on pediatric patients and found that the severity of bronchiectasis worsens as lung function deteriorates. Che-Chiu et al. also reported that all 13 patients in their study had bronchiectasis confirmed by CT scans, indicating that standard spirometry alone may not detect early structural lung changes in PID patients [55]. The remarkable effectiveness of IVIG replacement therapy in reducing respiratory infections and minimizing lung damage is well-documented [50, 113]. Notably, in this study, 85.7% of patients with PID received IVIG replacement therapy. This widespread use of IVIG therapy could explain the absence of significant differences in lung volumes (FVC) or forced expiratory flows (FEV_1, PEF, $FEF_{25-75\%)}$ between the two groups. Furthermore, compelling research has revealed a direct correlation between immunoglobulin levels and a slower decline in lung function [56].

It is crucial to consider the potential impact of age on pulmonary function in patients with PID. Jolles et al. noted a higher incidence of lung disease in adult patients with PID compared

to children with PID [114]. This variation could be due to several factors, such as increased exposure to pathogens, extended periods of untreated infections, delayed diagnoses, and other health conditions in adults. These factors help explain the preserved lung function in patients PID. Notably, 85.7% of our patients received IVIG replacement therapy, and 42.9% received prophylactic antibiotics [50, 113, 115, 116]. These interventions play a role in mitigating lung complications in our patient population. Therefore, evaluating lung function in patients with PID is critical for early detection of complications and improving their overall health outcomes.

Weakness in the respiratory muscles may be a factor in decreased exercise capacity and physical function. Assessment of respiratory muscle function yields essential information for clinical practice and is crucial for understanding symptom load, prognosis, and responsiveness to treatment [96]. There is no information about respiratory muscle involvement in patients with PID in literature. However, possible information may be drawn from studies regarding respiratory muscles in bronchiectasis and CF [61, 117-120]. Wang et al. reported weakened respiratory muscle strength in adult patients with bronchiectasis; and positively correlated expiratory muscle strength with FVC and exercise capacity. They also reported that patients with severe disease represent more weakened respiratory muscles [61]. Dunnink et al. reported decreased MIP in CF patients aged 26±7 years compared to reference values, whereas MEP remained preserved [119]. Arikan et al. reported that respiratory muscle strength was preserved in CF patients aged 15 (7–25) years [117]. In contrast, Dassios et al. reported that CF patients aged 14 (10–17) years with preserved pulmonary function have weakened respiratory muscle [118]. Moreover, Sovtic et al. reported a correlation between FEV_1 and MIP in CF patients aged 16.8±6.5 years, however MIP and exercise capacity was not related [120]. The significant decrease in MEP values indicates that expiratory muscle strength is particularly compromised in children with PID. This may influence several respiratory functions, such as coughing effectively and airway clearance, which are critical for respiratory infection prevention and preserving lung health [121]. The results of this first study provide valuable insights into respiratory muscle involevement in children with PID. Regular assessment of respiratory muscle strength in this population is recommended to guide clinical management and optimize patient outcomes.

The present study showed that the respiratory muscle endurance of patients with PID is preserved. Although not statistically different, the patients with PID had lower respiratory

endurance. A noteworthy proportion of children with PID (64.28%) had respiratory muscle endurance pressure below 80% of the expected value, which yields further investigation in adulthood of the patients with PID.

The changes in SpO_2 and dyspnea remained same between the patient and healthy children indicating that respiratory muscle endurance to exertion was similar. In contrast, research on CF has explored about respiratory muscle endurance extensively, with some studies reporting preserved [98] respiratory muscle endurance and others indicating a significant impairment [98, 122-124]. Vendrusculo et al. reported that patients with CF aged 14.0±2.7 years, despite having preserved pulmonary function, exhibited impaired respiratory muscle endurance. The study showed that increased airway resistance and airway obstruction lead to a higher respiratory workload, which, in turn, enhances respiratory muscle endurance due to the endurance exercise effect on these muscles [124]. Similarly, Keens et al. in their study on patients with CF aged 16±0.8 years and FEV_1% 66.5±4.5%, showed that respiratory muscle endurance is preserved, similar to us [122]. They stated that ventilation against chronic stress, as a result of the increase in respiratory work caused by airway obstruction, develops muscle adaptation and significantly increases endurance. On the contrary to our results, Leroy et al., in a study with 18 adult patients with CF aged 32±12.6 years and FEV_1% 44.1±18.8, reported a significant decrease in respiratory muscle endurance correlated with dyspnea. Suggesting that respiratory muscle endurance impairmen may be one of the determinants of dyspnea [123]. The severity of PID, the frequency of infections, chronic inflammation, malignancy, physical inactivity, and exercise capacity may all possibly contribute to impaired respiratory muscle endurance. Given the lack of research on respiratory muscle endurance in patients with PID, it is crucial to investigate this relationship further. Thus, performing respiratory muscle endurance measurements routinely is essential.

Primary immunodeficiencies may extend their impact beyond the respiratory system, affecting skeletal muscles throughout the body and leading to peripheral muscle weakness. This weakness can manifest in various ways and significantly impacts the quality of life for individuals with PIDs [60, 61]. The exact mechanisms underlying muscle weakness in patients with PIDs remain under investigation. However, insights can be drawn from similar conditions like bronchiectasis, COPD, and cancers. These conditions share common factors like chronic inflammation, oxidative stress, nutritional deficiencies, altered cytokine levels, and protein imbalances, all contributing to the loss of muscle strength and function [62]. The

current study's findings reveal weakness in peripheral muscle strength in patients with PID both upper and lower extremity muscles.

No previous information was reported whether peripheral muscle strength is affected or not in patients with PID. However, it is possible to compare the results of our findings with similar conditions as pediatric patients with CF and bronchiectasis. Unlike PID, there are many studies on CF and bronchiectasis [125-128]. Pinet et al. conducted a study and reported using an isokinetic system in 18 adult patients with CF aged 27.6±6.9 years, BMI 17.8±1.8 kg/m^2, and FEV_1% 39±15%, similar to our study, in which QF muscle strength is impaired [126]. Vendrusculo et al. conducted a study with patients with CF aged 15.9±6.5 years, measuring maximal exercise capacity and peripheral muscle strength. An association between peripheral muscle strength, exercise capacity, and the use of antibiotics was reported. Patients with reduced exercise capacity or those needing antibiotics had weakened peripheral muscle strength [128]. The 42.9% of our patients were using prophylactic antibiotics. Patients with PID are often prescribed prophylactic antibiotics, which may be associated with decreased muscle strength. To explore the association between antibiotic use and exercise capacity in patients with PID, further studies are needed. Troosters et al.[127] conducted a study on adult patients with CF aged 25±6 years, reporting weakened peripheral muscles and found no association between pulmonary function and QF muscle strength. Additionally, 56% of CF patients had lower QF muscle strength than expected. In accordance with the findings of Troosters et al. [127], the present study showed that 64.28% of patients with impaired QF muscle strength with PID with preserved pulmonary function. Our study suggests the need to evaluate peripheral muscle strength routinely in this patient population. Future research should explore the underlying mechanisms contributing to muscle weakness in PID. Factors such as chronic inflammation, reduced physical activity levels, and the direct effects of immune deficiency on muscle tissue need to be investigated. Additionally, intervention studies are warranted to assess the efficacy of various rehabilitation approaches, including resistance training and functional exercises.

Functional exercise capacity, the ability to perform daily physical activities, is a crucial factor in overall health and quality of life for individuals with PID [14]. Recurrent infections, complications of respiratory infections such as bronchiectasis, pneumonia, lung abscesses, and empyema, along with structural airway abnormalities, cause shortness of breath, fatigue, coughing, muscle weakness, and psychological factors, all of which limit participation in

exercise and physical activity [12, 68]. Unfortunately, this aspect has been largely unexplored in PID population. In adult patients with PID, there is one research investigating the impact of exercise [14], whereas studies in pediatric patients with PID are entirely lacking.

The present study's findings indicate that patients with PID have a decreased functional exercise capacity. The significantly shorter 6-MWT distance may be attributed to reduced physical activity levels and peripheral muscle weakness in PID patients, potentially impacting their ability to manage daily activities. These findings align with research on other chronic respiratory diseases as bronchiectasis and CF, which also report impaired functional exercise capacity [129-133]. Sami et al. [134] reported shorter 6-MWT distance in patients with non-CF bronchiectasis, comparing the disease's severity forms; they reported that BMI, FEV_1, and FEV_1/FVC were predictors of impact in SpO_2. Future studies evaluating their relationship with patients with PID should be conducted. Moreover, Sami et al reported higher 6-MWT distance 73.55±14.56% in patient with severe bronchiectasis than the patients with PID (66.75%).

Sowers et al. [14], in their study invastigating the impact of exercise and behaviors in adult patients with PID, reported that 41.32% of the patients had a loss of mobility and physical activity level. Physical limitations and potential psychological factors might create significant barriers to regular physical activity.

However, SpO_2 stability does not necessarily translate to similar exercise capacity. Other factors, such as cardiovascular function, muscle strength, and overall endurance, may be compromised in patients with PID. This is further supported by the contrasting HR findings between our study and Cunha et al.'s research on CF patients [79.4 ± 8.3% HR increase] [129]. Our study found a lower peak HR than healthy controls, with values falling within the submaximal range. These discrepancies highlight the potential for different mechanisms affecting functional exercise capacity in PID compared to other chronic diseases like CF and bronchiectasis.

Further research is crucial to understand the specific limitations contributing to reduced exercise capacity in patients with PID. In addition, future studies should investigate the role of cardiovascular function, muscle strength, deconditioning, and the impact of various PID

subtypes on exercise capacity. This comprehensive understanding will be vital for developing targeted interventions to improve exercise tolerance and overall quality of life in this patient population.

Another essential measure evaluated in patients with PID is maximal exercise capacity. Our findings unveiled significant impairments in several CPET parameters, highlighting potential limitations in maximal exercise capacity in this patient population. The findings of our study reveal reduced peak VO2kg, lower MET, HR, and SpO_2; meanwhile, $EqCO_2$ increased, and increase in the perception of dyspnea, fatigue, and QF fatigue in patients with PID.

While no studies have directly measured maximal exercise capacity in patients with PID, studies on bronchiectasis and CF, conditions often associated with frequent respiratory infections and inflammations comparable to PID, can provide useful insights. There are studies that reported impaired maximal exercise capacity in CF and non-CF bronchiectasis patients [135-137]. Yoseph et al. reported decreased peakVO_{2kg} in patients with CF (37.7±10.3 ml/min/kg) and non-CF bronchiectasis (35.3±10.8 ml/min/kg) [135], which were higher than our patients with PID (33.27±5.98 ml/min/kg). In contrast to our results, Yoseph et al. did not observe hypoxemia in the patients during the test. Which suggests that there may be potential impairment in patients with PID in oxygen delivery in working muscles during exercise. The disparity in SpO_2 results between our study and that of Yoseph et al. could be attributable to differences in the underlying pathophysiology of PID versus CF and non-CF bronchiectasis. Furthermore, Yoseph et al. reported similar O_2HR in the groups, the results are consistent with our findings in patients with PID suggesting a maximal cardiovascular effort during exercise [135]. Additionally, the particular immunological problems in PID may result in more severe systemic consequences that limit exercise capacity. Similar to our study, Moser et al. reported reduced VO_2 in patients with CF with no difference in RER, which was not influenced by exercise. [136]. Another study conducted by Stevens et al. [137], comparing children with chronic lung diseases to healthy children, reported lower exercise capacity and significant decrease in VO_{2peak}. Moreover, Stevens et al. reported no correlation between pulmonary function and VO_{2peak} in patients with lung diseases, which shows that exercise capacity limitations vary independently from pulmonary function. In contrast to our findings, Stevens et al. reported normal chronotropic responses in patients with chronic lung dieases. Lower HR values in patients with PID indicate

potential cardiovascular limitations which can lead to insufficient circulation and oxygenation during physical activity. The similarities between our findings and those of Stevens et al. regarding the independence of exercise capacity from pulmonary function highlight the complexities of exercise limitations in chronic conditions [137]. Chronic inflammation, recurrent infections, or immune system dysregulation may all contribute to cardiopulmonary limits in patients with PID, reducing overall exercise capacity.

Routine exercise testing in patients with PID is indicated to detect and control any limitations early. CPET should be part of a thorough examination for patients with PID, particularly those who have reported exercise intolerance. Future studies are required to investigate the underlying processes of decreased maximal exercise capacity in PID. Understanding the unique contributions of immune dysregulation, inflammation, and cardiopulmonary constraints will help guide interventions.

Children with chronic diseases exhibit distinct pathophysiological characteristics that impact their exercise tolerance and physical activity levels [74]. The combination of factors like recurrent infections, inflammation, autoimmunity, and malignancy might impact the physical activities in patients with PID, leading to a cycle of inactivity and further physical deconditioning [74]. Patients with PID displayed decreased active energy expenditure, number of daily steps, and average MET values. Regarding step count classification, more patients with PID were classified as inactive (57.1%) compared to healthy children (13.3%). Conversely, only 7.15% of PID patients were classified as highly active, compared to 20% of healthy children. Interestingly, total energy expenditure, physical activity duration exceeding 3 METs, and sleep duration were similar in patients and healthy children. This suggests that patients with PID may compensate for their reduced activity levels by engaging in more sedentary activities or spending more time lying down. Sedentary behavior is associated with both short- and long-term health issues [138]. This is the first study that provided valuable insight into physical activity levels in patients with PID using an objective measurement.

To present, studies examining physical activity and/or sedentary behavior in children with other respiratory disorders, such as asthma, cystic fibrosis, and bronchiectasis, have yielded contradictory results [139-146]. While some research indicates that children with respiratory diseases are less active than the general population, others find no difference [147, 148]. The

results from the study of Joschtel et al. [143] are similar to our findings; children with bronchiectasis were reported to have lower levels of physical activity with a total number of steps of 8229.5 (7458.8–9000.2). Moreover, the study reports 418.7 (399.5–437.9) minutes of laying down in patients with bronchiectasis, which is lower than our results of 528.50 (493.75-556) minutes of laying down in patients with PID. These findings imply that similarly patients with PID spent over 8 hours per day being sedentary. Potentially replacing these sedentary hours with light or moderate activities possibily enhance healthy life status in PID. Future studies should focus on determining the effectiveness of such interventions in children with chronic respiratory disease. Similar to our results, a study done by Aznar et al. in patients with CF with mean age 12 ± 3 years reported having low levels of physical activity levels [139]. Van Gent et al. found similar levels of physical activity in young children with both diagnosed and undiagnosed asthma, despite having preserved pulmonary function.[148]. Impaired exercise capacity, weakness in peripheral muscles, recurrent infections, and chronic inflammation all contribute to low physical activity levels in patients with PID. This study also emphasized the critical need to raise awareness of physical activity counseling for patients with PID.

Recurrent infections, chronic inflammation, malignancy, and autoimmunity combined in PID can have an impact on muscle oxygenation. In chronic diseases, the muscle oxidative capacity is impaired by many factors like inflammations, hypoxia, and physical inactivity [78]. The vicious cycle of recurrent infections and chronic inflammation fuels oxidative stress, damaging blood vessels and mitochondria. This combined effect impairs oxygen delivery and utilization within muscles. Additionally, immune dysregulation in PIDs disrupts endothelial cell function and reduces capillary density in muscle tissue, further compromising oxygen perfusion [76, 79].

During 6-MWT, there was a notable variance in SmO_{2max} and $SmO_{2avg\text{-}max}$, indicating a diminished capacity to extract oxygen from the blood flow during functional physical activity. Moreover, the difference in ΔSmO_2 suggests a change during minimal and peak muscle oxygen extraction in patients with PID. The similarity in values for resting (SmO_{2rest}), minimum (SmO_{2min}), average minimum ($SmO_{2avg\text{-}min}$), recovery ($SmO_{2recovery}$), and total hemoglobin (THb) parameters between the two groups suggests that the baseline muscle oxygenation and total hemoglobin concentration do not differ significantly.

Children with PID exhibited significantly lower resting oxygen saturation (SmO_{2rest}), peak oxygen saturation (SmO_{2max}) and $SmO_{2recovery-avg}$, compared to healthy children during CPET. Suggesting limitations in extracting oxygen from the blood flow in maximal exercise test. The noticeable difference in $SmO_{2revoery-avg}$, suggests a slower recovery of muscle oxygenation after maximal exercise capacity. Peak oxygen saturation (SmO_{2max}) during CPET was 50.90±12.30, meanwhile during 6-MWT the SmO_{2max} was 55.0±16.93. Indicating greater limitations in patients with PID under maximal exertion. THb parameters were found similar in both functional and maximal exercise test. There is no information in the literature on whether muscle oxygenation is impaired in patients with PID.

Coelho et al., in patients with CF similar age to our patients, reported lower muscle oxygenation and greater deoxyhaemoglobin concentration during the modified shuttle test. Moreover, they found a correlation between deoxygenation time and functional capacity [149]. In a study conducted by Saynor et al., a CPET was carried out using a cycle ergometer on patients with CF, found a relation between impaired exercise capacity and low muscle oxygen delivery [150]. Moreover, there is research showing no difference in muscle oxygenation in patients with CF [151]. Werkman et al. tested mild CF patients with stable clinical status using supine cycle ergometry with NIRS and 31-Phosphorus magnetic resonance spectroscopy (^{31P}MRS) to study muscle oxygenation and oxidative metabolism. However, the findings showed no difference in maximal exercise capacity, muscle oxygenation, or oxidative metabolism [151]. This study is the first to provide information about muscle oxygenation in patients with PID. Additional studies are necessary to gain deeper insights into the physiological changes in muscle oxygenation experienced by patients with PID during both functional and maximal physical exertion.

In the literature, it is known that patients with PID have lower health-related quality of life [81-84]. Disease complications, recurrent infections, chronic symptoms, and physical and financial burdens to treatment reduce HR-QOL. Patients with PID have an increased risk of complications that compromise their physical and mental health status [81-84]. There is currently no disease-specific questionnaire for PID that assesses the quality of life in the pediatric population. Additionally, limited research has been conducted on developing disease-specific HR-QOL questionnaires for adults [85, 86, 152].

Many studies reported impaired HRQoL in patients with PID [81-85, 153-155]. However, some studies reported similar quality of life with healthy children. The results of our PedsQL questionnaire, both child-reported and parent-reported, highlight the decreased quality of life in patients with PID.

Similar to our study, Ridao-Manonellas et al. [154], reported decreased quality of life in children with PID. School dimension received the poorest score by patients. On the contrary, to our results the mean score is higher and the physical dimension received the poorest score. Kuburovic et al. compared the quality of life in patients with PID children with juvenile idiopathic arthritis (JIA), and healthy children. They reported significantly lower PedsQL scores in patients with PID compared to those with JIA and healthy children. The psychosocial dimension scores for PID patients were also lower than those of healthy children and JIA patients [153]. Similar to our study, Ataeinia et al. reported decreased quality of life in patients with PID. They also reported no correlation between gender, age, scores and the type of PID [85].

The quality of life of patients with PID may be impacted by the chronic nature of these conditions, inadequate therapy, delayed diagnosis, and treatment side effects. Due to their medical conditions and requirement for monthly hospital visits, these patients participate in few social and regular activities and are more likely to miss work or school. All of which affect the HRQoL in this patient population [155, 156]. The results of our study suggest that the psychosocial and physical aspects of quality of life are significantly impacted in children with PID.

Limitations

One factor that could influence the results of our study can be the receiving of IVIG. Not all the patients were receiving IVIG treatment because of their stable medical condition. In the future studies exluding patients who do not receive IVIG treatment might give more specific results. Additionally, the heterogeneity within subgroup could be another possible factor influencing the results. Future studies focusing on specific subgroups need to be investigated.

6. CONCLUSION AND SUGGESTIONS

The most important results of our study, which aims to evaluate the maximal and functional exercise capacity, physical activity level, respiratory functions, respiratory and peripheral muscle strength, respiratory muscle endurance, muscle oxygenation, quality of life, and dyspnea of primary immunodeficiency patients, and compare them with healthy children reliability with highly valid evaluation methods;

The patients with primary immunodeficiency demonstrated a significant reduction in both functional and maximal exercise capacity. They showed lower physical activity levels, peripheral muscle weakness, impaired muscle oxygenation, and notably reduced quality of life. However, their pulmonary function, respiratory muscle strength, and endurance were well-preserved. This research stands out as the initial study to evaluate functional and maximal exercise capacity, respiratory muscle strength and endurance, peripheral muscle strength, physical activity levels, and muscle oxygenation using objective measurements.

According to the results of our study, our recommendations are;

1. In our study, although our patients were young, their functional and maximal exercise capacity, physical activity levels, and peripheral muscle strength were impaired. There were abnormalities in muscle oxygenation, and quality of life decreased. These findings underscore the necessity for early evaluation and intervention. Including these patients in comprehensive cardiopulmonary rehabilitation programs is essential to address these deficiencies and improve their overall health outcomes. Investigating the effects of rehabilitation is needed.
2. Patients with PID and healthy children showed a similar distribution in age, height, body weight, body mass index, and gender. These results show that patients with PID and healthy children otherwise constitute a suitable sample for the study regarding demographic data.
3. The results of our investigation showed that pulmonary function parameters between patients with PID and healthy children were statistically similar, the FEV_1/FV ratio was significantly lower in the PID group. 28.57% of the patients exhibited an obstructive defect, 14.29% had a mixed pattern, and 7.17% had a restrictive pattern. These findings indicate a tendency towards obstructive

pulmonary impairments in children with PID, highlighting the need for pulmonary care. It is necessary to carry out longitudinal research to investigate how children with PID's pulmonary function changes over time.

4. The results of our study indicate the similarity in respiratory muscle strength between patients with PID and healthy children, except the MEP (%) value is lower in the patient group. Notably, 42.86% of the patients had lower MIP values, and 21.43% had lower MEP values than 80% expected. Regular assessment of respiratory muscle strength can help detect the risk of weakness early. More studies need to be done to understand the effects of inspiratory and expiratory muscle training in this patient population.
5. The results of our study show that respiratory muscle endurance has been preserved in patients with PID. Further studies need to examine the presence of respiratory muscle endurance weakness in patients with PID, its causes, its relationship with pulmonary functions, and the relationship with IVIG treatment.
6. Our study measured peripheral muscle strength in patients with PID and healthy children using objective measurement. The results show that peripheral muscle strength has been affected in the patients. The causes and effects of weakness need to be further investigated. It is recommended to conduct longitudinal studies to investigate the progression of peripheral muscle weakness in children with PID and its impact on functional outcomes.
7. Our study shows a significant decrease in functional exercise capacity in patients with PID. All patients (100%) and six (40%) healthy children had lower 6-MWD than the 80% expected. Notably, patients with PID exhibited lower maximal heart rate and expected percentage, higher systolic blood pressure, and higher breathing frequency compared to healthy children. 6-MWT should be conducted routinely in patients with PID, and they need to be included in cardiopulmonary rehabilitation programs.
8. Patients with PID have an impaired maximal exercise capacity compared to healthy children. Our study found that patients have lower VO_{2kg}, MET, HR, and SpO_2. However, they have higher $EqCO_2$, Dyspnea, Fatigue, and QF fatigue perception. The results bring forth novel research regarding patients with PID. The effects of the disease on ventilatory, cardiac, and metabolic systems need to be further investigated.

9. The patient and healthy children had significant differences in physical activity parameters. Patients with PID showed lower average MET values, steps taken, and active energy expenditure, all indicators of decreased physical activity levels. On the other hand, the groups' overall energy expenditure, amount of physical activity, and amount of time spent lying down were similar. Additionally, there were notable differences in the physical activity level classifications across the groups based on the number of steps taken each day, with 57.1% of PID patients categorized as inactive. Building programs and providing physical activity counseling for this patient population is critical.
10. The muscle oxygenation of the quadriceps femoris during the 6-MWT and CPET test revealed significant differences between patients with PID and healthy children. Specifically, maximum muscle oxygen saturation was lower in patients than in healthy children. Total hemoglobin levels were similar between the groups. Future studies need to be carried out to understand the physiological effects of PID in perfusion and oxygen utilization.
11. Children with PID and healthy children's self-reported PedsQL questionnaire scores showed significant differences in psychosocial health, physical health aspects, and overall scores. Compared to healthy children, patients with PID reported lower scores in these domains, indicating a reduced quality of life. In line with the tendency of parents to report a worse quality of life, patients with PID had substantially lower parent-reported psychosocial health summary scores, physical health summary scores, and overall scores than healthy children. A multidisciplinary approach must be employed to address the issues of patients with PID. This study is an addition to the existing literature.

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ATTACHMENTS

Attachment 1. Ethical Approval Form

Evrak Tarih ve Sayısı: 05.04.2023-E.629133

T.C.
GAZİ ÜNİVERSİTESİ REKTÖRLÜĞÜ
Etik Komisyonu

Sayı : E-77082166-302.08.01-629133 05.04.2023
Konu : Bilimsel ve Eğitim Amaçlı

Dağıtım Yerlerine

Üniversitemiz Sağlık Bilimleri Enstitüsü Fizyoterapi ve Rehabilitasyon Ana Bilim Dalı **Yüksek Lisans Öğrencisi Riad BEJTA'nın, Prof. Dr. Meral BOŞNAK GÜÇLÜ'nün** danışmanlığında yürüttüğü ***"Primer İmmün Yetmezliği Olan Çocukların Egzersiz Kapasitesi, Fiziksel Aktivite Seviyesi ve Yaşam Kalitesinin Sağlıklılarla Karşılaştırılması"*** adlı tez çalışması ile ilgili konu Komisyonumuzun **04.04.2023** tarih ve **07** sayılı toplantısında görüşülmüş olup,

İlgilinin çalışmasının, yapılması planlanan yerlerden izin alınması koşuluyla yapılmasında etik açıdan bir sakınca bulunmadığına oybirliği ile karar verilmiş ve karara ilişkin imza listesi ekte gönderilmiştir.

Bilgilerinizi rica ederim.

Araştırma Kod No: 2023 - 464

Prof. Dr. İsmail KARAKAYA
Komisyon Başkanı

Ek:1 Liste
DAĞITIM
Gereği:
Sayın Prof. Dr. Meral BOŞNAK GÜÇLÜ

Bilgi:
Sağlık Bilimleri Enstitüsü Müdürlüğüne

Attachment 1. (continued) Ethical Approval Form

Evrak Tarih ve Sayısı: 05.04.2023-E.629733

GAZİ ÜNİVERSİTESİ
ETİK KOMİSYONU KATILIM LİSTESİ

TOPLANTI TARİHİ : 04.04.2023	TOPLANTI SAYISI : 07
ADI – SOYADI	İMZA
Prof. Dr. İsmail KARAKAYA BAŞKAN	
Prof.Dr.Zehra GÖÇMEN BAYKARA BAŞKAN YRD.	
Prof.Dr.C.Hakık BODUR	
Prof.Dr.Seçil ÖZKAN	
Prof.Dr.Cevriye TEMEL GENCER	
Prof.Dr.İlkay ULUTAŞ	
Prof.Dr.Aymdek GÖNENÇ	
Prof.Dr.Kemalettin DENİZ	
Prof.Dr.Makbule GEZMEN KARADAĞ	
Prof.Dr.İbyas OKUR	
Prof.Dr.Nihat KAFA	
Doç.Dr.Melek Gülşah ŞAHİN	
Doç.Dr. Gökhan DELİCEOĞLU	
Doç.Dr.Elvan İNCE AKA	

Attachment 2. Informed Volunteer Consent Form

Rev-2
25.01.2022

T.C.
GAZİ ÜNİVERSİTESİ
ETİK KOMİSYONU

KATILIMCILAR IÇIN BILGILENDIRILMIŞ GONULLU OLUR FORMU

Sizi, **Gazi Üniversitesi Etik Komisyonu**'ndan 04.04.2023 tarih / 07 sayı ile izin alınan* ve Prof. Dr. Meral BOŞNAK GÜÇLÜ ve Riad BEJTA tarafından yürütülen "Primer immün yetmezliği olan çocukların egzersiz kapasitesi, fiziksel aktivite seviyesi ve yaşam kalitesinin sağlıklılarla karşılaştırılması" başlıklı araştırmaya davet ediyoruz. Bu çalışmaya katılmak tamamen gönüllülük esasına dayanmaktadır. Çalışmaya katılmama veya katıldıktan sonra herhangi bir anda çalışmadan çıkma hakkına sahipsiniz. Bu çalışmaya katılmanız için sizden herhangi bir ücret istenmeyecektir. Çalışmaya katıldığınız için size bir ödeme yapılmayacaktır. Çalışmadan elde edilecek bilgiler tamamen araştırma amacı ile kullanılacak olup kişisel bilgileriniz gizli tutulacaktır.

*Gazi Üniversitesi Etik Komisyon izini alındıktan sonra doldurulamk kullanılacaktır.

Araştırmanın Amacı	Primer immün yetmezlik hastalarında fonksiyonel egzersiz kapasitesi, solunum fonksiyonları, fiziksel aktivite seviyesi, yaşam kalitesi, solunum kas kuvveti ve endurans, periferik kas kuvveti, maksimal egzersiz kapasitesi ve kas oksijenizasyonu sağlıklı bireylerle karşılaştırılmasıdır.
Araştırmanın Yöntemi	• Bu çalışma kapsamında size herhangi girişimsel bir uygulama yapılmayacaktır. • Tıbbi muayene, tüm medikal tedaviler Sağlık Bakanlığı Dr. Sami Ulus Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk İmmünoloji ve Allerji Hastalıkları bölümü hekimleri tarafından yapılacaktır. • Çalışmaya katılmanız durumunda toplamda iki yarım gün sürecek bir değerlendirme yapılacaktır. • Demografik ve fiziksel özellikleriniz (ad, soyad, yaş, cinsiyet, medeni durum, eğitim durumu, meslek, hastalık özgeçmişi, aile öyküsü, sigara kullanımı, boy, kilo, vücut kitle indeksi, kullanılan ilaçlar) hasta değerlendirme formuna kaydedilecektir. • Kardiyopulmoner rehabilitasyon dahilindeki tüm değerlendirmeleriniz fizyoterapistler tarafından yapılacaktır. • Çalışmada, oksijen tüketiminiz kardiyopulmoner egzersiz testi (KPET); fonksiyonel egzersiz kapasiteniz altı dakika yürüme testi; kas oksijenizasyonunuz kas oksijen monitörü; fiziksel aktivite seviyeniz çok sensörlü aktivite monitörü; solunum sistemi fonksiyonunuz solunum fonksiyon testi; solunum, bacak ve kol kas kuvvetiniz kas kuvvet ölçüm cihazları; solunum kaslarınızın dayanıklılığı solunum kas eğitim cihazı ile değerlendirilecektir. • Fiziksel aktivite seviyenizi değerlendirmek için kullanılan aktivite monitörü sağ kolunuza kesintisiz dört gün takılacak ve sadece banyo yaparken çıkarılacaktır. Dört günün sonunda monitör sizden teslim alınacaktır. • Yaşam kalitesi değerlendirilmesi için özel Türkçe anket ile yapılacaktır. • Çalışma sırasında kan basıncı, kalp hızı, solunum sayısı, oksijen doygunluğu gibi yaşamsal bulgularınız kaydedilecektir. • Değerlendirmeler sonrası tespit edilen problemlere yönelik rehabilitasyon uygulamaları planlanacaktır. • Araştırmaya özel ek bir tahlil istenmeyecektir
Araştırmanın Öngörülen Süresi (Başlama ve Bitiş Tarihi Başvurudaki Başlangıç ve Bitiş Tarihi ile Uyumlu Olmalıdır.)	01.05.2023-30.04.2024
Araştırmaya Katılması Beklenen Katılımcı/Gönüllü Sayısı	Araştırmaya katılma kriterlerini karşılayan ve katılmaya kabul eden kişiler katılımcı/gönüllü sayısını belirleyecektir. En az 52 kişi

Attachment 2. (continued) Informed volunteer consent form

Araştırmanın Yapılacağı Yerler	Gazi Üniversitesi Sağlık Bilimler Fakültesi Fizyoterapi ve Rehabilitasyon bölümü Kardiyopulmoner Ünitesi
Görüntü ve/veya ses kaydı alınacak mı?	Evet ☐ Hayır ☒

Tablo katılımcıların anlayabileceği biçimde, akademik dil kullanılmadan yazılacaktır.

KATILIMCI BEYANI

Yukarıda amacı ve içeriği belirtilen bu araştırma ile ilgili bilgiler tarafıma aktarıldı. Bu bilgilerden sonra araştırmaya katılımcı olarak davet edildim. Bu çalışmaya katılmayı kabul ettiğim takdirde gerek araştırma yürütülürken gerekse yayımlandığında kimliğimin gizli tutulacağı konusunda güvence aldım. Bana ait verilerin kullanımına izin veriyorum. Araştırma sonuçlarının eğitim ve bilimsel amaçlarla kullanımı sırasında kişisel bilgilerimin dikkatle korunacağı konusunda bana yeterli güven verildi. Araştırmanın yürütülmesi sırasında herhangi bir sebep göstermeden çekilebilirim. Araştırma için yapılacak harcamalarla ilgili herhangi bir parasal sorumluluk altına girmiyorum. Bana herhangi bir ödeme yapılmayacaktır. Araştırma ile ilgili bana yapılan tüm açıklamaları ayrıntılarıyla anlamış bulunmaktayım. Bu çalışmaya hiçbir baskı altında kalmadan kendi bireysel onayım ile katılıyorum. İmzalı bu form kağıdının bir kopyası bana verilecektir.

Araştırma yürütücüsü(Tez çalışmalarında Danışman tarafından imzalanacaktır.)

Adı ve Soyadı	Prof.Dr. Meral BOŞNAK GÜÇLÜ	Tarih ve İmza
Adres ve telefonu	Gazi Üniversitesi Sağlık Bilimleri Fakültesi Fizyoterapi ve Rehabilitasyon Anabilim Dalı Emek mah. Bişkek Cad. 6. Cad. 81. sokak) No:2 06490 Çankaya/ANKARA	

Katılımcı

Adı ve Soyadı		Tarih ve İmza
Adres ve telefonu		

Velayet veya Vesayet Altındaki Katılımcılar için Veli/Vasi

Adı ve Soyadı		Tarih ve İmza
Adres ve telefonu		

RESUME

Personal Information

Surname, Name : BEJTA, Riad

Nationality : Kosovo

Education

Degree	Educational institution	Graduation Date
Masters	Gazi Üniversitesi / Physiotherapy and Rehabilitation	Continues
Bachelors	University of Prishtina / Physiotherapy Department	2019

Work Experience

Year	Place	Job
2020-2021	Gjilan, Kosovo	Physiotherapist

Foreign Languages

English, Turkish, Albanian, Serbian

Publications

R Bejta, M Boşnak Güçlü, B Yöleri, C Aytekin "1. Eskişehir Fizyoterapi ve Rehabilitasyon Kongresi "Fizyoterapi ve Rehabilitasyonda Yenilikçi Yaklaşımlar" dahilinde bildiri kitapçığındaki "Primer İmmün Yetmezliği Olan Çocukların Egzersiz Kapasitesi, Solunum Fonksiyonları Ve Nefes Darlığının Sağlıklılarla Karşılaştırılması", Journal of Exercise Therapy and Rehabilitation. 2023;Sup (2) Bildiri No: S13-2, Eskişehir, Türkiye

Bejta R. Kavalcı Kol B. "COVID-19 Geçirmiş Astımlı Hastada Kardiyopulmoner Rehabilitasyon" Vakalarla Kardiyopulmoner Rehabilitasyonda Güncel Yaklaşımlar, Prof. Dr. Meral Boşnak Güçlü, Editör, Nobel Yayınevı, Ankara, ss. 133-151, 2023

R Bejta, M Boşnak Güçlü “Cardiopulmonary rehabilitation in Covid-19: A case report”, The 2nd International Congress of Physiotherapy abstract booklet May 2023: 45-46, Prishtina, Kosovo

Hobbies

Reading, travelling, coffee

GAZİLİ OLMAK AYRICALIKTIR..