Archive Volume 92, Issue 1, January 2022

Analysis of Increasing D-Dimer, Decreasing P/F Ratio and Rox Index As Predictors Of HFNC Therapy Failure In Covid-19 Patients (https://ijrp.org/paper_detail/2709)
Pages: 7 , Published Online: 10 Jan 2022
DOI: 10.47119/IJRP100921120222740 (https://doi.org/10.47119/IJRP100921120222740) , Views: 299 , Downlaod: 169

Paper Dov

The Correlation of Length of Stay in Intensive Care with Duration of Ventilator Support Usage toward Post-COVID-19 Syndrome Incidence and Mortality in COVID-19 Survivors (https://ijrp.org/paper_detail/2698)
Pages: 7 , Published Online: 08 Jan 2022
DOI: 10.47119/IJRP100921120222725 (https://doi.org/10.47119/IJRP100921120222725) , Views: 294 , Downlaod: 175

Paper Dov

Effects of Home-based Incentive Spirometry on FEV1, FVC, 6-MWT, Control Status and Quality of Life of Asthma Patients (https://ijrp.org/paper_detail/2697)
Pages: 9 , Published Online: 08 Jan 2022
DOI: 10.47119/IJRP100921120222724 (https://doi.org/10.47119/IJRP100921120222724) , Views: 364 , Downlaod: 187

Paper Dov

Rehabilitation of Vascular Transtibial Amputee Patients with Type 2 Diabetes Mellitus and Peripheral Artery Disease: A Case Report (https://ijrp.org/paper_detail/2695)
Pages: 6 , Published Online: 08 Jan 2022
DOI: 10.47119/IJRP100921120222722 (https://doi.org/10.47119/IJRP100921120222722) , Views: 282 , Downlaod: 159

Paper Dov

Guillain Barre Syndrome in Children : Case Report (https://ijrp.org/paper_detail/2694)
Pages: 9 , Published Online: 08 Jan 2022
DOI: 10.47119/IJRP100921120222721 (https://doi.org/10.47119/IJRP100921120222721) , Views: 293 , Downlaod: 163

Paper Dov

Effect of McConnell Patelar Taping on Walking Speed, Step Length, and Stride Length in Sub acute Stroke Patient (https://ijrp.org/paper_detail/2692)
Pages: 8 , Published Online: 07 Jan 2022
DOI: 10.47119/IJRP100921120222718 (https://doi.org/10.47119/IJRP100921120222718) , Views: 256 , Downlaod: 149

Paper Dov

Increase in Knowledge Among Young Adult Participants Regarding Nutrition after the Webinar Serotonin 2021 (https://ijrp.org/paper_detail/2689)
Pages: 7 , Published Online: 07 Jan 2022
DOI: 10.47119/IJRP100921120222708 (https://doi.org/10.47119/IJRP100921120222708) , Views: 287 , Downlaod: 163

Paper Dov

id=108)

Vol. 107, Issue 1, August (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=107)

Vol. 106, Issue 1, August (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=106)

Vol. 105, Issue 1, July (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=105)

Vol. 104, Issue 1, July (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=104)

Vol. 103, Issue 1, June (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=103)

Vol. 102, Issue 1, June (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=102)

Vol. 101, Issue 1, May (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=101)

Vol. 100, Issue 1, May (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=100)

Vol. 99, Issue 1, April (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=99)

Vol. 98, Issue 1, April (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=98)

Vol. 97, Issue 1, March (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=97)

Vol. 96, Issue 1, March (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=96)

Vol. 95, Issue 1, February (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=95)

Vol. 94, Issue 1, February (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=94)

Vol. 93, Issue 1, January

Effect of high-intensity interval training on treadmill exercise with changes in inclination on Heart Rate Variability in overweight/obese men (https://ijrp.org/paper_detail/2688)
Pages: 7 , Published Online: 06 Jan 2022
DOI: 10.47119/IJRP100921120222705 (https://doi.org/10.47119/IJRP100921120222705) , Views: 343 , Downlaod: 175

Effect of high-intensity interval training on treadmill exercise with changes in inclination on serum IL-6 levels in overweight/obese men (https://ijrp.org/paper_detail/2687)
Pages: 6 , Published Online: 06 Jan 2022
DOI: 10.47119/IJRP100921120222703 (https://doi.org/10.47119/IJRP100921120222703) , Views: 309 , Downlaod: 168

A patient with Rotor syndrome and coronary artery disease: is it a coincidentalor related? (https://ijrp.org/paper_detail/2685)
Pages: 9 , Published Online: 06 Jan 2022
DOI: 10.47119/IJRP100921120222699 (https://doi.org/10.47119/IJRP100921120222699) , Views: 257 , Downlaod: 169

Risk Factors for Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in Dr. Soetomo General Hospital Surabaya (https://ijrp.org/paper_detail/2681)
Pages: 8 , Published Online: 06 Jan 2022
DOI: 10.47119/IJRP100921120222695 (https://doi.org/10.47119/IJRP100921120222695) , Views: 436 , Downlaod: 222

Relationship Between Disease Severity and Balance Function in Patients with Myasthenia Gravis (https://ijrp.org/paper_detail/2679)
Pages: 7 , Published Online: 06 Jan 2022
DOI: 10.47119/IJRP100921120222693 (https://doi.org/10.47119/IJRP100921120222693) , Views: 337 , Downlaod: 169

Descriptive Analysis of Participants Before and After Attending the Workshop ?Meditation as a Form of Relaxation? METHADONE 2021 (https://ijrp.org/paper_detail/2678)
Pages: 11 , Published Online: 05 Jan 2022
DOI: 10.47119/IJRP100921120222692 (https://doi.org/10.47119/IJRP100921120222692) , Views: 292 , Downlaod: 171

The Effect of 99 Percent Edible Bird's Nest (EBN) Extract Suplementation on Serum Interleukin-1 Beta (IL-1?) Levels in Health Workers Treating Covid-19 Cases in Dr. Soetomo General Hospital (https://ijrp.org/paper_detail/2676)
Pages: 9 , Published Online: 05 Jan 2022
DOI: 10.47119/IJRP100921120222690 (https://doi.org/10.47119/IJRP100921120222690) , Views: 309 , Downlaod: 192

Determination Of The Age Of Blood Spots In Adults With Hemoglobin Levels Below Normal Based On The Natural Color System (Ncs) Standard Card (https://ijrp.org/paper_detail/2672)
Pages: 13 , Published Online: 05 Jan 2022
DOI: 10.47119/IJRP100921120222684 (https://doi.org/10.47119/IJRP100921120222684) , Views: 329 , Downlaod: 153

Prevalence of Malaria among Pregnant Women in Nigeria: A Scope Review of Literature (https://ijrp.org/paper_detail/2671)
Pages: 6 , Published Online: 04 Jan 2022
DOI: 10.47119/IJRP100921120222683 (https://doi.org/10.47119/IJRP100921120222683) , Views: 348 , Downlaod: 196

Relationship between Neutrophil Lymphocyte Ratio in Children with H. Pylori and Non H. Pylori Gastritis (https://ijrp.org/paper_detail/2670)
Pages: 10 , Published Online: 04 Jan 2022
DOI: 10.47119/IJRP100921120222680 (https://doi.org/10.47119/IJRP100921120222680) , Views: 177 , Downlaod: 145

The Effect of Calcium on Decreasing Primary Dysmenorrhea Pain Intensity: Literature Review (https://ijrp.org/paper_detail/2658)
Pages: 6 , Published Online: 03 Jan 2022
DOI: 10.47119/IJRP100921120222664 (https://doi.org/10.47119/IJRP100921120222664) , Views: 223 ,

(https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=93)

Vol. 92, Issue 1, January (https://ijrp.org/paper/Medicine--Health---Food/3/archive?id=92)

+ 2021

+ 2020

+ 2019

+ 2018

+ 2017

Join as an Editor / Reviewer (https://ijrp.org/join)

Downlaod: 174

COMPARISON OF PRISM IV AND PELOD 2 SCORE AS PREDICTOR OF MORTALITY IN CRITICALLY ILL CHILDREN IN ADAM MALIK GENERAL HOSPITAL (https://ijrp.org/paper_detail/2657)
Pages: 12 , Published Online: 03 Jan 2022
DOI: 10.47119/IJRP100921120222663 (https://doi.org/10.47119/IJRP100921120222663) , Views: 222 , Downlaod: 170

Paper Dov

Comparison The Effects of Endurance and Resistance Exercise On Static and Dynamic Balance in Obese Adolescent Boys (https://ijrp.org/paper_detail/2655)
Pages: 13 , Published Online: 03 Jan 2022
DOI: 10.47119/IJRP100921120222661 (https://doi.org/10.47119/IJRP100921120222661) , Views: 213 , Downlaod: 191

Paper Dov

Risk Factors of Retinopathy of Prematurity in Tertiary Hospital (https://ijrp.org/paper_detail/2653)
Pages: 9 , Published Online: 03 Jan 2022
DOI: 10.47119/IJRP100921120222659 (https://doi.org/10.47119/IJRP100921120222659) , Views: 232 , Downlaod: 146

Paper Dov

Profile Of Children With Guillan Barre Syndrome In RSUP Haji Adam Malik Medan: Events In 5 Years (https://ijrp.org/paper_detail/2652)
Pages: 10 , Published Online: 03 Jan 2022
DOI: 10.47119/IJRP100921120222658 (https://doi.org/10.47119/IJRP100921120222658) , Views: 205 , Downlaod: 176

Paper Dov

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Archive (https://ijrp.org/archive) Contact Us (https://ijrp.org/contact)

Stress Level during Thesis Writing in Pandemic Covid-19 among Midwife Students, Universitas Airlangga Surabaya (https://ijrp.org/paper_detail/2643)
Pages: 6 , Published Online: 31 Dec 2021
DOI: 10.47119/IJRP100921120222712 (https://doi.org/10.47119/IJRP100921120222712) , Views: 232 , Downlaod: 196

Paper Dov

Hyperbaric oxygen therapy as a potential therapy for new-onset diabetes mellitus in post-COVID-19 syndrome: current evidence (https://ijrp.org/paper_detail/2642)
Pages: 11 , Published Online: 31 Dec 2021
DOI: 10.47119/IJRP100921120222654 (https://doi.org/10.47119/IJRP100921120222654) , Views: 299 , Downlaod: 197

Paper Dov

C-Reactive Protein Based on Injury Level and Physical Activity Level of Chronic Spinal Cord Injury Patient (https://ijrp.org/paper_detail/2641)
Pages: 10 , Published Online: 31 Dec 2021
DOI: 10.47119/IJRP100921120222647 (https://doi.org/10.47119/IJRP100921120222647) , Views: 298 , Downlaod: 184

Paper Dov

Hand Dermatitis Due to Hand Hygiene During the Pandemic Covid 19 (https://ijrp.org/paper_detail/2639)
Pages: 8 , Published Online: 31 Dec 2021
DOI: 10.47119/IJRP100921120222710 (https://doi.org/10.47119/IJRP100921120222710) , Views: 232 , Downlaod: 196

Paper Dov

The Effect of Feeding Patterns on the Nutritional Status of Elementary School Children During the COVID-19 Pandemic In Tuban Regency, East Java (https://ijrp.org/paper_detail/2638)
Pages: 6 , Published Online: 31 Dec 2021
DOI: 10.47119/IJRP100921120222714 (https://doi.org/10.47119/IJRP100921120222714) , Views: 226 , Downlaod: 153

Paper Dov

Description of Midwife Anxiety Levels in Antenatal Care Services during the COVID-19 Pandemic **(https://ijrp.org/paper_detail/2635)**
Pages: 6 , **Published Online:** 31 Dec 2021
DOI: 10.47119/IJRP100921120222728 (https://doi.org/10.47119/IJRP100921120222728) , **Views:** 196 , **Downlaod:** 142

THE QUALITY OF LIFE ON MODE OF DELIVERY : A LITERATURE REVIEW **(https://ijrp.org/paper_detail/2633)**
Pages: 6 , **Published Online:** 31 Dec 2021
DOI: 10.47119/IJRP100921120222711 (https://doi.org/10.47119/IJRP100921120222711) , **Views:** 230 , **Downlaod:** 168

Description of Maternal Age and Premature Occurrence in RSUD Sidoarjo For The Period October-November 2021 **(https://ijrp.org/paper_detail/2632)**
Pages: 5 , **Published Online:** 31 Dec 2021
DOI: 10.47119/IJRP100921120222717 (https://doi.org/10.47119/IJRP100921120222717) , **Views:** 209 , **Downlaod:** 151

Characteristics Of Pulmonary Arterial Hypertension in Children with Acyanotic Congenital Heart Disease **(https://ijrp.org/paper_detail/2631)**
Pages: 11 , **Published Online:** 31 Dec 2021
DOI: 10.47119/IJRP100921120222726 (https://doi.org/10.47119/IJRP100921120222726) , **Views:** 215 , **Downlaod:** 171

The Potential of Hyperbaric Oxygen Therapy Against Codeine Addiction Reduction **(https://ijrp.org/paper_detail/2629)**
Pages: 9 , **Published Online:** 31 Dec 2021
DOI: 10.47119/IJRP100921120222706 (https://doi.org/10.47119/IJRP100921120222706) , **Views:** 226 , **Downlaod:** 202

Relationship Between Immunization Status and Stunting in Toddler aged 2 ? 5 Years in Banjarejo Village **(https://ijrp.org/paper_detail/2628)**
Pages: 5 , **Published Online:** 30 Dec 2021
DOI: 10.47119/IJRP100921120222754 (https://doi.org/10.47119/IJRP100921120222754) , **Views:** 183 , **Downlaod:** 133

Education?s Impact On Children?s Knowledge Levels About COVID-19 And How To Prevent It In The Surabaya City **(https://ijrp.org/paper_detail/2627)**
Pages: 6 , **Published Online:** 30 Dec 2021
DOI: 10.47119/IJRP100921120222753 (https://doi.org/10.47119/IJRP100921120222753) , **Views:** 191 , **Downlaod:** 147

Vancomycin Monotherapy vs Alternative Antibiotics for MRSA Patients: A Systematic Review **(https://ijrp.org/paper_detail/2626)**
Pages: 12 , **Published Online:** 30 Dec 2021
DOI: 10.47119/IJRP100921120222689 (https://doi.org/10.47119/IJRP100921120222689) , **Views:** 293 , **Downlaod:** 246

Clinical Characteristics and Survival in Non-Epithelial Ovarian Cancer **(https://ijrp.org/paper_detail/2623)**
Pages: 16 , **Published Online:** 30 Dec 2021
DOI: 10.47119/IJRP100921120222751 (https://doi.org/10.47119/IJRP100921120222751) , **Views:** 172 , **Downlaod:** 134

Lipid Nanoparticles Delivery of CRISPR/Cas9 Targeting PCSK9 and ANGTPL3 as New Therapeutic Gene Editing Modalities for Potential Long-Lasting Treatment Of Dyslipidemia **(https://ijrp.org/paper_detail/2622)**
Pages: 11 , **Published Online:** 30 Dec 2021
DOI: 10.47119/IJRP100921120222750 (https://doi.org/10.47119/IJRP100921120222750) , **Views:** 156 , **Downlaod:** 153

ANALYSIS OF THE RELATIONSHIP OF KNOWLEDGE AND ATTITUDE OF PREGNANT MOTHERS WITH UTILIZATION OF MCH BOOK **(https://ijrp.org/paper_detail/2621)**
Pages: 8 , **Published Online:** 30 Dec 2021

DOI: 10.47119/IJRP100921120222748 (https://doi.org/10.47119/IJRP100921120222748) , Views: 166 ,
Downlaod: 144

Electroencephalogram (EEG) Features of Post-Stroke Seizure Patients in the Department of Neurology, Dr. Soetomo General Hospital Surabaya (https://ijrp.org/paper_detail/2619)
Pages: 15 , Published Online: 30 Dec 2021
DOI: 10.47119/IJRP100921120222648 (https://doi.org/10.47119/IJRP100921120222648) , Views: 252 ,
Downlaod: 192

Paper Dov

Increased Knowledge About COVID-19 Vaccination of Non-Medical College Students in Surabaya (https://ijrp.org/paper_detail/2618)
Pages: 7 , Published Online: 30 Dec 2021
DOI: 10.47119/IJRP100921120222669 (https://doi.org/10.47119/IJRP100921120222669) , Views: 263 ,
Downlaod: 171

Paper Dov

Knowledge, Attitude, Practice, and Concerns of Non-Medical Students in Surabaya Against Covid-19 Vaccination (https://ijrp.org/paper_detail/2616)
Pages: 11 , Published Online: 29 Dec 2021
DOI: 10.47119/IJRP100921120222670 (https://doi.org/10.47119/IJRP100921120222670) , Views: 277 ,
Downlaod: 216

Paper Dov

Potential Neurogenesis and Neuroprotective Effects of Epigallocatechin-3-gallate (EGCG) in Green Tea (Camellia sinensis) Through Microglia M2 Induction Process and NLRP3 Inhibition as an Innovation for Ischemic Stroke Adjuvant Therapy: A Review (https://ijrp.org/paper_detail/2614)
Pages: 8 , Published Online: 29 Dec 2021
DOI: 10.47119/IJRP100921120222656 (https://doi.org/10.47119/IJRP100921120222656) , Views: 235 ,
Downlaod: 180

Paper Dov

Profile of Chronic Rhinosinusitis Patients that Undergo Functional Endoscopic Sinus Surgery at Dr. Soetomo General Hospital Year 2015-2019 (https://ijrp.org/paper_detail/2613)
Pages: 9 , Published Online: 29 Dec 2021
DOI: 10.47119/IJRP100921120222668 (https://doi.org/10.47119/IJRP100921120222668) , Views: 268 ,
Downlaod: 169

Paper Dov

Clinical And Hematological Profile Of Febrile Neutropenia In Pediatric Patients Who Suffered From Malignancy At Dr. Soetomo General Academic Hospital Surabaya (https://ijrp.org/paper_detail/2612)
Pages: 7 , Published Online: 29 Dec 2021
DOI: 10.47119/IJRP100921120222667 (https://doi.org/10.47119/IJRP100921120222667) , Views: 268 ,
Downlaod: 173

Paper Dov

Risk Factors of Birth Asphyxia : Literature Review (https://ijrp.org/paper_detail/2609)
Pages: 10 , Published Online: 29 Dec 2021
DOI: 10.47119/IJRP100921120222729 (https://doi.org/10.47119/IJRP100921120222729) , Views: 210 ,
Downlaod: 165

Paper Dov

Antibiotic Sensitivity Pattern of Escherichia coli from Catheter- Associated Urinary Tract Infections (CAUTI) at Intensive Care Unit (https://ijrp.org/paper_detail/2608)
Pages: 7 , Published Online: 29 Dec 2021
DOI: 10.47119/IJRP100921120222655 (https://doi.org/10.47119/IJRP100921120222655) , Views: 213 ,
Downlaod: 157

Paper Dov

Cost Pattern Comparison between Survivor-and Non-survivor of Mechanically-Ventilated COVID-19 Patients (https://ijrp.org/paper_detail/2607)
Pages: 8 , Published Online: 28 Dec 2021
DOI: 10.47119/IJRP100921120222688 (https://doi.org/10.47119/IJRP100921120222688) , Views: 237 ,
Downlaod: 169

Paper Dov

Basic Immunization During The Covid-19 Pandemic : A Literature Review (https://ijrp.org/paper_detail/2606)
Pages: 5 , Published Online: 28 Dec 2021
DOI: 10.47119/IJRP100921120222715 (https://doi.org/10.47119/IJRP100921120222715) , Views: 274 ,
Downlaod: 177

Paper Dov

Overview of the Pattern of Complementary Feeding to Stunting Toddlers Age 6-24 Months in the Tampo Banyuwangi Community Health Center Work Area (https://ijrp.org/paper_detail/2605)

Paper Dov

Pages: 8 , **Published Online:** 28 Dec 2021
DOI: 10.47119/IJRP100921120222713 (https://doi.org/10.47119/IJRP100921120222713) , **Views:** 266 ,
Downlaod: 207

Effects of Thiamazole Administration on Weight Changes in Children with Graves' Disease at H. Adam Malik General Hospital Medan, Indonesia (https://ijrp.org/paper_detail/2601)
Pages: 6 , **Published Online:** 27 Dec 2021
DOI: 10.47119/IJRP100921120222702 (https://doi.org/10.47119/IJRP100921120222702) , **Views:** 191 ,
Downlaod: 178

Paper Dov

Relationship of Ferritin, Interleukin-8, and D-Dimer Levels with PaO2/FiO2 Ratio and Mortality in ARDS COVID-19 (https://ijrp.org/paper_detail/2600)
Pages: 10 , **Published Online:** 26 Dec 2021
DOI: 10.47119/IJRP100921120222682 (https://doi.org/10.47119/IJRP100921120222682) , **Views:** 237 ,
Downlaod: 176

Paper Dov

Cyberbullying And Suicidal Behavior (https://ijrp.org/paper_detail/2597)
Pages: 12 , **Published Online:** 25 Dec 2021
DOI: 10.47119/IJRP100921120222653 (https://doi.org/10.47119/IJRP100921120222653) , **Views:** 242 ,
Downlaod: 215

Paper Dov

Description of the Anxiety Level of Pregnant Women Regarding Antenatal Care Services During The COVID-19 Pandemic: Literature Review (https://ijrp.org/paper_detail/2596)
Pages: 8 , **Published Online:** 25 Dec 2021
DOI: 10.47119/IJRP100921120222727 (https://doi.org/10.47119/IJRP100921120222727) , **Views:** 233 ,
Downlaod: 144

Paper Dov

No Correlation Between Anemia in Third Trimester Pregnant Women and Preeclampsia/Eclampsia inDr. Seotomo Hospital Surabaya (https://ijrp.org/paper_detail/2595)
Pages: 8 , **Published Online:** 24 Dec 2021
DOI: 10.47119/IJRP100921120222707 (https://doi.org/10.47119/IJRP100921120222707) , **Views:** 257 ,
Downlaod: 181

Paper Dov

Correlation between Absolute Neutrophil Count Level and Helicobacter Pylori Infection in Pediatric Gastritis (https://ijrp.org/paper_detail/2577)
Pages: 9 , **Published Online:** 18 Dec 2021
DOI: 10.47119/IJRP100921120222720 (https://doi.org/10.47119/IJRP100921120222720) , **Views:** 168 ,
Downlaod: 133

Paper Dov

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Faq (https://ijrp.org/faq)

Archive

Volume 123 Issue 1 April 2023 ((https://ijrp.org/archive/123)
Volume 122 Issue 1 April 2023 ((https://ijrp.org/archive/122)
Volume 121 Issue 1 March 2023 ((https://ijrp.org/archive/121)
Volume 120 Issue 1 March 2023 (

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Characteristics Of Pulmonary Arterial Hypertension in Children with Acyanotic Congenital Heart Disease

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Abstract

Background: Congenital heart disease is the leading cause of death in infants related to birth defects and can cause chronic defects [1]. The most common complication is pulmonary hypertension (PH). The worst manifestation of PAH is Eisenmenger syndrome. If it has manifested into Eisenmenger syndrome, the defect in CHD cannot be corrected [2,3]. Research on the characteristics of PAH in CHD needs to be known for better treatment.
Methods: This is a descriptive study in pediatric patients with acyanotic congenital heart disease. In this research we used medical records. Data analysis was carried out descriptively.
Results: The results of this study showed that the prevalence of PAH was 7.08%, and most of the patients were toddlers (33 patients or 57.9%) and female (38 patients of 66.7%). The most common diagnosis of CHD lesions was ASD, found in 19 patients (33.3%). Most patients came with severe PAH conditions. Pharmacological therapy in the form of sildenafil was mostly given. The most common symptoms were shortness of breath and murmurs on physical examination. There was no relationship between intervention variables, pharmacological therapy, and mortality and between diagnosis of CHD and severity of PAH.
Conclusion: Although the prevalence of PAH was not high in this study, the mortality rate was quite high. It is necessary to educate the parents of patients with congenital heart disease so that further complications can be prevented early on. It is also necessary to make services better to improve the nutritional status of patients. Pharmacological therapy and intervention measures need to be reviewed and improved to reduce mortality in patients.

Keywords : pulmonary hypertension;pulmonary arterial hypertension, ; congenital heart defect ; acyanotic ; pediatric.

1. Main text

1. Introduction

Congenital heart disease is the leading cause of death in infants related to birth defects, and it may result in chronic defects. It has caused Indonesia to incur high treatment costs. The incidence of this disease is estimated at up to 43,200 cases out of 4.8 million live births (9:1000 live births) annually. The most common type of CHD is left-to-right shunt acyanotic CHD. If not immediately corrected, it will cause complications, which are often found in the lungs. Complications of left-to-right shunt acyanotic CHD include pulmonary hypertension (HP) [4,5]

In Indonesia, it is estimated that there are 25,000 patients who have pulmonary hypertension [6]. The prevalence of HP caused by CHD is 5% to 10% in adult patients. In children, HP occurs in 2 to 16 cases per one million children [7]. The research conducted by RSUP Dr. Sardjito revealed that as many as 77.1% of 1,102 patients had pulmonary hypertension [8]. Pulmonary hypertension is classified into five groups based on its pathophysiology, etiology, clinical features, hemodynamic characteristics, and therapeutic management. Pulmonary hypertension in CHD is classified as pulmonary arterial hypertension.

Pulmonary arterial hypertension in pediatric patients is rare. In pediatric cases, it is commonly found in patients who are with CHD, especially acyanotic CHD with septal defects [9,10]. Pulmonary arterial hypertension, if not treated immediately, can cause pressure to increase, leading to a right-to-left shunt reversion in a condition known as Eisenmenger syndrome. Eisenmenger syndrome is the most severe form of pulmonary arterial hypertension. In Indonesia, especially in the province of Yogyakarta, in 2018, it was found that 68.7% of 800 patients had PAH and Eisenmenger syndrome at a young age. If Eisenmenger syndrome manifestation has started, the defect in CHD cannot be corrected and it will even require an intervention in the form of heart-lung organ transplantation [2,3].

It is necessary to conduct research to determine the characteristics of pediatric patients with pulmonary arterial hypertension, especially in the city of Surabaya. Through this study, the characteristics of pulmonary arterial hypertension in pediatric patients with left-to-right shunt acyanotic CHD in need of a surgical intervention were investigated, which included basic characteristics, degree of PAH, clinical symptoms, physical examination, and prevalence of PAH. Patient mortality rate and the relationship between several variables were also examined.

2. Materials and Methods

Research with retrospective descriptive method was conducted at RSUD Dr. Soetomo Surabaya using the medical records of patients from the pediatrics department registered from January to December 2019. The population of this study was all acyanotic congenital heart disease patients aged 0–18 years with pulmonary arterial hypertension at RSUD Dr. Soetomo Surabaya in the time frame from January to December 2019. The inclusion criteria set for this research were patients aged 0 to 18 years and having left-to-right shunt acyanotic CHD. Meanwhile, patients with cyanotic congenital heart disease obstructive lesions and incomplete medical record data were excluded.

Each patient's information regarding basic characteristics, nutritional status, diagnosis of acyanotic congenital heart disease, pulmonary arterial hypertension degree, pharmacological therapy, intervention measures, and accompanying diseases as well as information on patient mortality after receiving treatment was collected from medical records.

3. Results

There were a total of 804 children with acyanotic congenital heart disease. The incidence of acyanotic CHD without PAH well exceeded that of acyanotic CHD with PAH (747 patients vs 57 patients, or 92.91% vs 7.08%).

Table 1. Basic Characteristics of Patients

Characteristics	**N (57)**	**%**
Age		
Toddler < 5 years	33	57.9
Child	19	33.3
Teen	5	8.8
Sex		
Male	19	33.3
Female	38	66.7

Diagnostic of Acyanotic CHD		
ASD	19	33.3
VSD	17	29.8
PDA	4	7.0
AVSD	1	1.8
ASD & VSD	7	12.3
VSD & PDA	4	7.0
ASD & PDA	2	3.5
ASD, VSD, & PDA	3	5.3
Degree of Pulmonary Hypertension		
Mild	8	14.0
Moderate	11	19.3
Severe	38	66.7
Nutritional Status		
Age < 5 y.o		
Severely wasted	11	19.3
Wasted	8	14
Normal	10	10
Overweight	2	3.5
Obese	2	3.5
Age > 5 y.o.		
Severely thin	6	10.5
Thin	6	10.5
Normal	11	19.3
Obese	1	1.8

According to Table 1, under-five acyanotic congenital heart disease patients with pulmonary artery hypertension were most commonly found at RSUD Dr. Seotomo Surabaya in the period January–December 2019, and female patients outnumbered their male counterparts (38 patients or 66.7%). The most common type of left-to-right shunt acyanotic congenital heart disease found in the patients was atrial septal defect (19 patients or 33.3%). From observation it was also found that some patients were diagnosed with more than one type of congenital heart disease: 2 patients (3.5%) were diagnosed with ASD and PDA, 4 patients (7%) with VSD and PDA, 7 patients (12.3%) with ASD and VSD, and 3 patients (5.3%) with all the three of ASD, VSD, and PDA.

Most of the patients (38 patients or 66.7%) were found to have a severe degree of disease. We tried to identify the relationship between degree of PAH and diagnosis of congenital heart disease, but we found no relationship between the two variables.

Tabel 2. Clinical symptoms

Symptoms	**N**	**%**

Breathlessness	34	59.6
Cough	22	38.6
Fever	20	35.1
Shortness of breath during activity	6	10.5
Cyanosis during activity	6	10.5
Loss of weight	6	10.5
Cyanosis	5	8.8
Cold	4	7
Vomit	4	7
Pale	2	3.5
Seizure	2	3.5
Blue from birth	1	1.8
Angina	1	1.8
No symptoms	8	14

From Tabel 2 we can see that the five clinical symptoms often found in patients were breathlessness, cough, fever, shortness of breath when doing strenuous activities, and cyanosis when doing activities. However, there were 8 patients (14%) who came to the hospital without any clinical symptoms.

Tabel 3. Physical Examination

Physical	**N (%)**
Murmur	29 (50.9)
Thorax retraction	22 (38.6)
Dyspnea	13 (22.8)
Anemia	11 (19.3)
Ronchi	8 (14)
Gallop	6 (10.5)
Delirium consciousness	5 (8.8)
Cyanosis	4 (7)
Icterus	3 (5.3)
Clubbing finger	2 (3.5)
Stridor	1 (1.8)
Nostril breath	1 (1.8)
Acral Cyanosis	1 (1.8)
Wheezing	1 (1.8)
Hepatomegaly	1 (1.8)
Normal	15 (26.3)

The three most common results of physical examination were murmurs, thoracic retractions, and dyspnea. Murmurs were present in 29 patients (50.9%), followed by thoracic retractions in 22 patients (38.6%) and dyspnea in 13 patients (22.8%). Nonetheless, in 15 patients (26.3%) the results were within normal limits.

Tabel 4. Co-morbidities

Co-morbidities	**N**	**%**
Pneumonia	16	28.0
Rheumatic Heart Disease	9	15.8
Acute Kidney Failure	2	3.5
Asthma	1	1.8
Hypothiroid	1	1.8
Atrial Fibrilation	1	1.8
Down Syndrome	1	1.8
Hydrocephalus	1	1.8
Acute tonsilitis	1	1.8
Umbilical Hernia	1	1.8
Atresia & Stenosis Rectum	1	1.8
Cellulitis& Lymphangitis	1	1.8
Hepatitis	1	1.8
Without co-morbidities	27	47.4

The most common co-morbidity was pneumonia, which occurred in 16 patients (28%), followed by rheumatic heart disease in 9 patients (15.8%). Patients without co-morbidities were also found quite a lot, numbering 27 (47.4%).

Tabel 5. PAH Spesific Treatment

	Drug	**N**	**%**
PAH Spesific Therapy	Sildenafil	34	59.6
	Sildenafil +Dorner	3	5.3
	Dorner	1	1.8
	No Medication	19	33.3

Patients coming to the hospital were treated in either of two ways, namely pharmacological drugs and intervention.

Based on Table 5, it was found that of a total of 57 patients most were given sildenafil pharmacological therapy (34 patients or 59.6%). Three patients received a specific combination therapy for PAH of sildenafil and Dorner (35.1%) and one other (1.8%) received a specific therapy for HAP of Dorner. Another 19 patients were not treated for pulmonary arterial hypertension.

Tabel 6. Heart Failure Symptoms Treatment

	Drug	**N**	**%**
Heart Failure Symptoms Therapy	Furosemid	20	35.1
	Spironolakton	16	28.1
	Digoxin	3	5.3
	Dobutamin	3	5.3
	Lisionapril	19	33.3
	Captopril	4	7
	Bisoprolol	1	1.8

According to Table 6, some patients received a drug therapy for symptoms of heart failure. The therapy given is not only of one type of drug. The most frequently administered drugs were furosemide (in 20 patients or 35.1%), lisionapril (in 19 patients or 33.3%), and spironolactone (in 16 patients or 28.1%).

Tabel 7 Intervention Procedure

Intervention Procedure	**N**	**%**
Yes	23	40.4
No	34	59.6
Total	57	100
Intervention Procedure	N	%
Transcatheter	8	34.8
Surgical Operation	11	47.8
Transcatheter & Surgical Operation	4	17.4
Total	23	100

According to Table 7, most acyanotic congenital heart disease pediatric patients with PAH did not receive any intervention (34 patients or 59.6%), while 23 patients (40.4%) did.

The intervention given could be in the form of transcatheter (in 8 patients or 34.8%) or surgery according to the diagnosis of congenital heart disease (in 11 patients or 47.8%). Another 4 patients (17.4%) received both interventions.

A total of 45 patients came home alive, 27 of whom (47.3%) lived without correction in their heart and 18 (31.6%) did with recovery after being given intervention measures for their congenital heart disease. Meanwhile, 12 other patients (21.1%) died.

We tried to find a correlation between intervention procedure in patients and mortality, but we found no relationship between the two. It was also found that there was no correlation between the administration of pharmacological therapy and mortality.

4. Discussion

The incidence of pulmonary arterial hypertension in acyanotic CHD was 7.08%. A similar number was also found in a study in the Netherlands, in which the incidence of PAH in adult CHD patients was found to be 4.2% [11]. Meanwhile, the research at RSUD Dr. Moewardi Surakarta showed that the incidence of PAH in children with acyanotic CHD was 56.7% [12].

4.1. Basic Characteristics

Most patients were at the age of under 5 years (33 patients or 57.9%). A similar case was also found by Vongpatanasin et al. [13], where 80% of PDA and VSD patients developed Eisenmenger syndrome, which is the most severe manifestation of PAH, in infancy. In Yogyakarta province it was found that 68.7% of 800 patients had PAH and Eisenmenger syndrome at a young age [3]. This finding could be because the diagnosis of CHD is usually made in childhood at 1 week to 1 month early in life [14].

In this study, the data obtained showed that of 57 left-to-right acyanotic CHD pediatric patients with PAH, 38 were female (66.7%) and 19 were male (33.3%). Other research also showed that pulmonary arterial hypertension is always found in more women than men. PAH in CHD was found in 60% of female patients [10]. In the UK and USA, female PAH patients made up 70% and 80% of all patients, respectively. There is also a general consensus that women are at a greater risk for PAH based on research that showed that the ratio of women to men in PAH group was 3:1 [15,16]. Several theories that are thought to be associated with the high incidence of PAH in left-to-right shunt acyanotic CHD in women are BMP, spontaneous closure of the defect, and biologic artery diameter [17].

ASD diagnoses were more common in child patients with pulmonary arterial hypertension than VSD. This is in contrast to that found by Pascall in the UK. He found that pulmonary artery hypertension was the most common in VSD congenital heart disease [10,14]. In this study several patients were found to be with more than one diagnosis. For instance, seven patients were diagnosed with ASD and VSD at once. The same thing was also found in China, in which 10 out of 56 patients had more than one diagnosis of CHD. Six of those 10 were discovered to have both ASD and VSD [18]. More ASD cases were found in this study probably because ASD tends to be asymptomatic. Therefore, ASD was undetected at an early stage and only found when complications occurred. These complications included pulmonary arterial hypertension [19].

PAH was mostly found in patients at a severe degree (38 patients or 66.7%). This could be because 16 of the 57 patients also had more than one type of septal defect, which of course would result in greater right-to-left heart blood flow. The size of the defect affected the degree of PAH, in which case large defects in ASD would result in a severe degree of PAH [10].

Good nutritional status (normal) was mostly found in patients aged 5–18 years, while poor nutritional status (severely wasted) was mostly found in patients at the age of 0–5 years. The same thing was also found in

Enugu and a previous study conducted at RSUD Dr. Soetomo Surabaya in 2012: pulmonary arterial hypertension increased the risk for wasting in CHD and caused lower heights and weights in pediatric patients than when PAH is non-existent [20,21]. Infants have a higher risk of developing malnutrition [22]. Patients aged over 5 years may have received early intervention so that malnutrition can be prevented [21].

4.2. Clinical Symptoms

The most common clinical symptom found in this study was shortness of breath, which could be due to a co-morbid disease that was mostly found in the patients in this study, namely pneumonia. This co-morbid disease was found in 16 patients. Shortness of breath was also found in Abassia Chest Hospital in Egypt [23]. Research in Turkey found the same symptoms with 52% of WHO FC III because of shortness of breath [8,24].

4.3. Physical Examination

In this study at RSUD Dr. Soetomo Surabaya, the 3 most common results found were murmurs, retractions on the thorax, and no physical abnormalities. Murmurs are sounds caused by turbulence in the blood flow in the heart. In pulmonary arterial hypertension there is regurgitation of the tricuspid valve due to right ventricular dilatation. This dilation is caused by the right ventricle not having enough pressure to push blood into the lungs which have too high a pressure [25,26]. This correlates with the findings of this study, that most of the patients had severe pulmonary arterial hypertension.

The retractions of the thorax were found to be due to difficulty in breathing, which was a clinical symptom in 38 patients in this study; this symptom urged the use of the chest muscles to help breathe [27].

4.4. Co-morbidities

In this study, the most common co-morbidity found in patients was pneumonia (in 16 patients). In addition, the number of patients without co-morbidities was also found to be quite large (27 patients). The same thing was also found in RSUP Dr. Djamil in Padang and RSUP Dr. Hasan Sadikin in Bandung: pneumonia was the most common co-morbidity found in congenital heart disease. Lung infections in patients can be due to malnutrition [5,28], which is also quite common in this study. Malnutrition in patients can increase the risk of infection and death [22].

4.5. PAH Spesific Treatment

Patients in this study received specific PAH therapy and treatment for symptoms of heart failure. The specific therapy often given is sildenafil. The same thing was also found in Poland, in which sildenafil was the most widely used [29]. The use of sildenafil in CHD children with PAH can increase oxyhemoglobin saturation and exercise capacity without significant side effects. In addition to providing minimal side effects, sildenafil is also sold for an affordable price. In a study of 25 children with PAH associated with chronic lung disease (including bronchopulmonary dysplasia, CHD, PPHN, and pulmonary hypoplasia), 88% showed improvement in echocardiographic measurements of pulmonary hypertension (HP) after a mean duration of sildenafil treatment of 40 days [30,31].

4.6. Intervention Procedure

Most of the patients did not receive any intervention. Performing surgery on patients with pulmonary arterial hypertension has risks. In this study where many patients came with severe PAH, there was a risk of a pulmonary hypertension crisis after surgery, which could accelerate the disease progression and the onset of right ventricular failure [32,33]. This reason might underlie why in this study left-to-right shunt acyanotic CHD patients with PAH more often did not receive any intervention.

Forty-five patients were discharged alive after receiving treatment from RSUD Dr. Soetomo Surabaya, 18 of whom recovered after receiving intervention. Meanwhile, 12 other patients died. Congenital heart disease with pulmonary arterial hypertension has a worse prognosis. The mortality rate in PAH-CHD is said to be quite high and has been reported more frequently than other etiologies of PAH [33]. Based on observations of medical records, patient deaths can be caused by either of the following two things: heart failure and septic shock.

5. Conclusion

In conclusion, this study provides information on the characteristics of acyanotic congenital heart disease pediatric patients with PAH at RSUD Dr. Soetomo Surabaya Indonesia from January to December 2019, especially those aged 0 to 18 years. Toddler, female patients with a severe degree of PAH and ASD defect were the most common patients. Most under-five patients had poor nutritional status, while many of those aged 5–18 years had good nutritional status. The most common symptoms were shortness of breath and murmurs on physical examination. Sildenafil was widely used, but intervention procedure was mostly not given. Although the prevalence of PAH-CHD in this study was not high, the mortality rate was quite high. It is considered necessary to conduct further research on pulmonary arterial hypertension in congenital heart disease involving a longer period of time using primary data and cross-sectional analytical methods. It is also necessary to educate the parents of patients with congenital heart disease so that further complications can be prevented early on as well as to make services better to improve the nutritional status of patients. Pharmacological therapy and intervention measures need also to be reviewed and improved to reduce mortality in patients.

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