Fernando Suparregui Dias[1], Clarice Sampaio Alho[2], Caroline Schwartz Henkin[3], Juliano Cé Coelho[3], Mateus Chissini Paganella[3], Rodrigo Morais de Siqueira[3], Fernanda Stringhi[4], Michelle Eidt[4], Virgínia Távora[5]

Genetic susceptibility in acute lung injury and acute respiratory distress syndrome

Suscetibilidade genética na lesão pulmonar aguda e síndrome da angústia respiratória aguda

1. Professor - Faculdade de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul - PUCRS - Porto Alegre (RS), Brazil.
2. PhD, Professor - Faculdade de Biociências da Pontifícia Universidade Católica do Rio Grande do Sul - PUCRS - Porto Alegre (RS), Brazil.
3. Graduation Student – Medicine - Faculdade de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul - PUCRS - Porto Alegre (RS), Brazil.
4. Resident Physician - Internal Medicine - Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul - PUCRS - Porto Alegre (RS), Brazil.
5. Physician – General Intensive Care Unit - Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul - PUCRS - Porto Alegre (RS), Brazil.

Received from Faculdade de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul - PUCRS - Porto Alegre (RS), Brazil.

Submitted on April 30, 2009
Accepted on December 23, 2009

Author for correspondence:
Fernando Suparregui Dias
Av. Ipiranga 6690 – Conj. 620 – Jardim Botânico
CEP: 90610-000 - Porto Alegre (RS), Brazil.
Phone/Fax: +55 51 3336-0304
E-mail: fersdias@via-rs.net

ABSTRACT

Acute lung injury and its most severe presentation, acute respiratory distress syndrome, are a common denominator for several diseases which can lead to exaggerated lung inflammation. In the last years this variability has been ascribed, at least partially, to genetic issues. This study aims to review the role of the main genes involved in acute lung injury and acute respiratory distress syndrome susceptibility, morbidity and mortality. By search on PubMed and LiLACS databases, using the key words acute lung injury, acute respiratory distress syndrome and adult acute respiratory distress syndrome in combination with genetic polymorphisms, 69 papers were selected, from which 38 were included in this review. Were also considered relevant articles extracted from the reference lists in the articles selected from the databases. Genetic polymorphisms are gene variations in at least 1% population. These gene variations may influence the inflammatory response mediators' expression, directly affecting the susceptibility to acute lung injury, the intensity of lung parenchyma inflammation, the development clinical course and outcome. Association studies reproducible in large populations will definitely allow genomics to be included into the diagnostic and therapeutic armamentarium for acute lung injury/acute respiratory distress syndrome patients.

Keywords: Lung injury; Respiratory distress syndrome, adult; Polymorphism, genetic

INTRODUCTION

Acute lung injury (ALI) and its major expression, acute respiratory distress syndrome (ARDS) are a common denominator for an array of illnesses able do trigger intensive pulmonary inflammatory response. These factors are considered primary when the lung injury starts at the epithelial end and secondary when starts at the alveolar-capillary barrier endothelial end.[1,2]

Epidemiological studies have shown considerable variability in ALI/ARDS incidence, with a yearly figures of 78.9 per 100,000 in the United States of America (USA),[3] 13.5 in Scandinavian,[4] 16 in Scotland[5] and 28 in Australia.[6] Nevertheless several risk factors may trigger the syndrome,[1,2] its expression and mortality are very variable.[7] One of the reasons explaining these differences may exactly reside on the impact of different risk factors on the inflammatory response.[8]

In the recent years, several genomic studies have shown an association between critical illness and genetic determinants, leading to a deeper un-

derstanding of pathophysiological mechanisms, particularly in sepsis/septic shock and ALI/ARDS. An important issue in ALI and ARDS is why some patients die from uncontrolled inflammation or sepsis, while others recover without major issues. This could be explained, at least partially, by that cellular events involved in inflammation mediation, tissue injury and repair, are controlled at a molecular level, and may not be completely explained without considering the genes and their products participating in this response.[9] In experimental trials, for instance, it was shown that the genetic profile expression in lung injury is specific for the injury type. In rat models, dos Santos et al.[10] documented that gene expression in ALI induced by LPS is different from that induced by alveolar hyperdistension. This change occurs early in ventilator induced lung injury (VILI) by high tidal volume, leading to proinflammatory mediators genes expression.[11] There are evidences that humoral and cellular immune response is subject to polymorphic genetic control, which could explain the diversity of manifestations, outcomes and the risk of being chronic among patients with a same illness. This picture is due to gene polymorphisms, which are gene variations in at least 1% population.[12]

In ALI/ARDS several candidate genes were associated to susceptibility, clinical course and outcomes. The role of these genes is related to inflammation, immu-

Chart 1 – Acute lung injury/acute respiratory distress syndrome associated genes

Author	Gene	Polymorphism	ALI/ARDS Association
Gong MN, et al.[17]	TNF-α	-308G>A	↑ mortality
	TNF-β	TNFB12	No mortality effect
Flores C, et al.[19]	IL-6	six 5' IL-6 SNPs -1363 to +4835	Haplotype GGGAAC ↑ susceptibility
Hildebrand F, et al.[21]	IL-8	-251A>T	↑ MV time
Gong MN, et al.[23]	IL-10	-1082G>A	Genotype GG ↑ susceptibility < 52 years ↓ DMOS and 60 days mortality
Schroeder O, et al.[22]	IL-10	-1082G>A	↓ susceptibility
Gong MN, et al.[27]	MBL-2	SNPs at 52, 54, 57 codons	Homozygotes 54BB ↑ susceptibility, severity, DMOS and mortality
Gao L, et al.[28]	Myosin light chain kinase (*MYLK)*	51 SNPs	Specific haplotypes gene 5' and 3' in different populations ↑ susceptibility
Bajwa EK, et al.[31]	PBEF	-1001G>T -1543T>C	-1001G>T ↑ susceptibility -1543T>C better outcome
Zhai R, et al.[33]	IκB-α	-881A>G, -826C>T, -297C>T	Haplotype GTC ↑ ARDS risk in Caucasians, particularly male
Adamzik M, et al.[34]	NFKB1	I/D -94ATTG	Affects ALI severity No mortality effect
Arcaroli JJ, et al.[36]	EC-SOD	rs4691, rs5321, rs5360, rs5955, rs5982	Haplotype GCCT ↓ ALI and mortality
Arcaroli JJ, et al.[38]	Urokinase	rs2227562, rs2227564, rs2227566, rs2227571, rs4065	Haplotype CGCCCC Risk factor ↑ mortality ↑ MV time
Adamzik M, et al.[39]	Fator V Leiden	Arg506Gln	↓ mortality in heterozygotes
Marshall MP, et al.[41]	ACE	I/D	Allele D associated with susceptibility and mortality
Jerng JS, et al.[43]	ACE	I/D	Genotype II best survival likelihood; allele D not associated with ↑ mortality in Chinese
Villar J, et al.[44]	ACE	I/D	No ARDS susceptibility or mortality association
Adamzik M, et al.[42]	ACE	I/D	Genotype DD ↑ risk of death
		AGT -6A>G	AGT -6A>G no susceptibility of mortality change
Medford AR, et al.[45]	VEGF	936C>T	Genotypes CT and TT more frequently associated with ARDS risk of death
Gong MN, et al.[46]	SFTPB	SNP no intron 4	↑ susceptibility in women ↑ primary ALI in women
Lin Z, et al.[47]	SP-A1, SP-A2, SP-B, SP-D	SP-B Thr13Ile	↑ ARDS susceptibility
Frerking I, et al.[48]	CC16	-26G>A	No susceptibility of outcome effect

ALI = acute lung injury; ARDS = acute respiratory distress syndrome.

ne response, vascular permeability, vascular tonus, repair, chemotaxis, cell motility and coagulation (Chart 1). From a practical stand point, the intensivist wants to know if a genetic marker may identify some clues, such as which patients would be more susceptible to develop ALI/ARDS, which patients could have a better response to a given treatment, and individual patients' prognosis.[7]

Considering that ALI/ARDS is consequence of another illnesses, has high mortality, involve long recovery and considerable costs, this study aims to review the main genes and polymorphic variations associated with ALI/ARDS incidence, morbidity and mortality.

This literature review was based on PubMed (National Library of Medicine and National Institute of Health – USA), LiLACS and relevant references mentioned on articles extracted from the research. The search was made using the keywords acute lung injury, acute respiratory distress syndrome, adult acute respiratory distress syndrome, combined with genetic polymorphisms considering only adult patients. Sixty nine articles were found, and after excluding editorials, reviews and genetic polymorphism in other diseases, the 38 remainder studies were included in the review. Were also considered the relevant articles extracted from the references in the database selected articles.

STUDIES OF CANDIDATE GENES AND ALI/ARDS ASSOCIATION

As ALI/ARDS are not based on a single etiology, genomic association studies in this field is a challenge task. The main objectives of identifying genetic markers in this syndrome is the determination of the susceptibility, prognosis and patients who could benefit from a given treatment.[7] The coclusion of human genome sequencing, listed 1.4 million single nucleotide polymorphisms (SNP), most of the variations occurring in genome regions not encoding protein products.[13] A SNP is a DNA change which represents the variation in one single base and is used to describe inter-individuals genetic variation.[7] When these SNPs occur in protein encoding regions, they may affect the effectiveness of this protein or gene function.[14]

The study of a gene expression or function by its phenotype analysis is useful in genetic diseases with classical Mendelian inheritance. This method is not suitable in ALI/ARDS, as multiple interactions of different genes and countless risk factors interact. Due to this difficulty, candidate genes case-control studies are the most common approach in ALI/ARDS susceptibility related factors. In these studies, a genetic variation has its genotype determined in a population where phenotypic information is available (ALI/ARDS). If a correlation between the study genotype and phenotype exists, it is assumed that there is an association between the genetic variation and the illness.[7]

Another way to identify candidate genes is by the microarrays technique. This technique determines the degree of a given gene expression by measuring mRNA (messenger ribonucleic acid). In summary, it consists in preparing a recipient for the genes of interest DNA with (1) isolation from a tissue cells mRNA; (2) cDNA generation by reverse transcription; (3) cDNA hybridization with the array DNA; (4) generation of array images by laser assisted optical digitalization.[15] However, as ALI/ARDS is a complex condition, specific genes changes probably do not fully explain all physiological derangements. The wide phenotypic range, incomplete penetrancy, interactions from genetics and environment and, potential for loci heterogeneity make difficult the genetic evaluation this syndrome.[16] Additionally, there is no possibility of isolating the cells from the affected tissue during the ALI/ARDS to be informative in the microarrays study. The main genetic polymorphisms associated with ALI/ARDS are shown in chart 1, and a glossary of currently used terms in shown in chart 2.

GENES RELATED TO INFLAMMATION, IMMUNE RESPONSE, OXIDATIVE STRESS AND COAGULATION

Cytokines have a fundamental role in local and systemic inflammatory response secondary to infection or inflammatory condition. The tumoral necrosis factor α (TNF-α) is a key cytokine in the inflammatory cascade, and one of the main mediators for sepsis and ALI/ARDS. The gene encoding TNF-α is at the chromosome 6, near to other genes encoding other cytokines, with an essential role for the cell cycle.[12] The polymorphism -308G>A in the TNF-α promoter gene, and TNFB1/2 in the TNF-β gene are associated with increased TNF-α synthesis.[17] In a case-control study with 441 Caucasian controls and 212 cases admitted with ALI/ARDS risk factors, the authors identified an association between the allele -308A and 60 days mortality, being this association more distinct in patients below 67 years-old. The TNFB polymorphism did not show

Chart 2 – Genomic medicine glossary

Term	Meaning
Allele	A gene variant version
Alu	DNA sequence constituted of about 200 nucleotides known by restriction endonuclease *Alu*I, frequently scattered repeated in the human genome.
Nitrogenated base	Adenine (A), Thymine (T), Cytosine (C) e Guanine (G)
cDNA	DNA segment complementary to messenger RNA
Encoding	Codons readings for protein synthesis
Codon	A three-base sequence of DNA or RNA that specifies a single amino acid.
DNA	Molecule formed by two nucleotide chains (pentose, phosphate and nitrogenated base) organized as helix
Exon	Intra-gene sequence, which after transcription remains on mRNA
Gene	DNA transcribing RNA segment
Candidate gene	Gene which changes and variants may give susceptibility to a given characteristic
Genotyping	Determination of the allele/gene types the patient inherited for some loci
Genotype	Diploid allele/genes set inherited for some loci
Haplotype	Haploid set of genetic variants inherited for a given locus
Heterozygote	Condition where the zygote was formed by two different allele/genes
Homozygote	Condition where the zygote was formed by two identical alleles/genes
Locus	A specific site where a gene (or a gene portion) is located in a chromosome
Microarrays	DNA sequence arrangements able to identify expressed (transcribed) genes depending on the tissue or physiological status or organs and individuals development
mRNA (messenger RNA)	A molecule formed by a nucleotide chain (pentose, phosphate and nitrogenated base) synthesized from a gene
Nucleotide	DNA and RNA former monomer constituted by pentose, phosphate and nitrogenated base
PCR (Polymerase Chain Reaction)	Technology allowing to synthesize DNA segments copies using temperature cycles
Polymorphism	Variable forms of a DNA sequence in a same locus. Are considered polymorphic forms already involving at least 1% population. Polymorphic variants may involve size or sequence
Promoter	DNA sequence preceding the region to be transcribed and promoting transcription
SNP (Single Nucleotide Polymorphism)	Replacement of one single nucleotide in a given position extending for at least 1% population.
Transcription	Process by which a gene is used as a mold for RNA molecules synthesis

association with mortality.[17]

The association between interleukin (IL)-6, a potent proinflammatory cytokine and ALI/ARDS shows conflicting results, at least regarding the SNP -174G>C. Although some authors have found an association between IL-6 gene with ALI/ARDS susceptibility,[18] this was not confirmed by others.[19] However, studying 20 SNPs in IL-6 gene, Flores et al[19] found an association between the haplotype GGGAAC and ALI/ARDS occurrence.

Also, IL-8 is one important mediator in ALI/ARDS pathogenesis. In ARDS patients' bronchoalveolar lavage (BAL), IL-8 levels are significantly increased and show association with ARDS development in the population at risk.[20] In studies of the association between IL-8 gene SNP -251A>T and ALI/ARDS, those bearing the -251A allele had more IL-8 synthesis and patients with the genotype -251AA needed mechanic ventilation (MV) for a relatively longer time.[21]

The SNP -1082GG genotype, in the IL-10 promoter gene is associated with reduced acute respiratory failure risk in trauma patients.[22] In ARDS patients, the genotype -1082GG is associated with lower admission severity, lower organ dysfunction degree and mortality.[23]

MBL (Mannose Binding Lectin) is a standard recognition protein, important in complement system and phagocytosis inducing opsonins activation.[24] The MBL protein is encoded by the MBL-2 gene (mannose binding lectin-2), at the chromosome 10. The circulating MBL

levels depend on three SNPs on codons 52 (rs5030737), 54 (rs1800450) and 57 (rs1800451, on the exon 1 and one SNP in the -221 position (MBLXY; rs7096202).[25] Exon 1 allele variants are known as D, B and C, respectively, while the wild allele is known as A. Exon 1 allele variants and the allele X in the MBLXY polymorphism are associated with serum MBL levels deficiency, particularly in homozygote individuals for rare allele variants.[26] A case-control study evaluated 212 Caucasian ARDS patients and 442 controls, hypothesizing that the X allele of MBLXY polymorphism and the MBL2 gene codons 52, 54 and 57 variants D, B and C are associated with increased ARDS susceptibility and mortality.[27] Homozygote for 54B allele variation (54BB) had increased admission severity, increased septic shock and ARDS likelihood compared with heterozygote and wild allele homozygote. The association with ARDS was specially marked on septic shock patients. In ARDS patients, the genotype 54BB was associated with increased number of organ dysfunctions and mortality.[27]

Among the macrophage produced mediators, the macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine with important role on endotoxemic response.[28] In 506 sepsis subjects DNA samples, both with sepsis-induced ALI and healthy controls, there was no correlation between individual SNPs and sepsis or ALI. An association was found between the haplotypes located in the MIF gene 3' region and sepsis and ALI susceptibility.[28]

The pre-B-cell colony-enhancing factor (PBEF), also know as visfatin, is an originally isolated from lymphocytes isolated cytokine.[29] PBEF expression is increased in human ALI animal models.[30] The genetics role for ARDS development was studied in 787 at risk and 375 established syndrome patients. The PBEF gene -1001T>G polymorphic variation was associated with increased susceptibility and mortality risk, while the -1543C>T polymorphism was associated with better outcomes.[31]

The κ-B nuclear factor (NF-κB) has an important role in inflammatory response, regulating several genes and inflammation mediators' expression, as adhesion molecules and cytokines. In non-stimulated cells, NF-κ-B is found in its inactive form in cytoplasm, I-κB (NFKBIA). When stimulated, NFKBIA is rapidly degraded and translocated to the nucleus, aiming to activate the target genes expression.[32] The GTC haplotype of NFKBIA gene is associated with increased ARDS risk in Caucasians, particularly in male and primary lung injury patients.[33] An insertion/deletion polymorphysim (ID) in the NFKB1 gene affects ARDS severity without influencing mortality.[34]

Oxygen free radicals (O_2FR) are produced in ischemia-reperfusion conditions. For protecting from the harmful effects these molecules, cells produce antioxidants which, by interacting with O_2FR generate less active products. Superoxyde dismutase (SOD) is one of the cell protecting antioxidant enzymes.[35] Extra-cellular (EC) SOD is largely expressed in the lungs, playing an important role in inflammation and oxidative stress regulation. In humans, the SOD gene is at the chromosome 4, and a SNP occurs in an encoder region resulting from an Arginine replacement for a Glycine. The end-product is a 10-fold increase in EC-SOD levels.[36] In addition to this change, at least three other were already identified as having important effects on ALI patients phenotype: in a 157 Caucasian patients population, those with GCCT haplotype had reduced lung inflammation, MV time and mortality.[36]

Urokinase is a serine protease acting on plasminogen clivation to form plasmin, a potent fibrinolytic mediator.[37] The urokinase gene is at the chromosome 10. In an association study, 98% of this gene haplotype were analyzed. The CGCCCC haplotype showed association with 60 days mortality and MV-free days, being a risk factor for unfavorable outcomes.[38]

The C protein pathway prevents exaggerated blood coagulation cascade activation, protecting against inadvertent clot formation by Va and VIIIa factors inactivation. Leiden factor V SNP changes this natural anticoagulation pathway normal activity to produce factor Va resistant to activated C protein inactivation. In ARDS patients, heterozygote subjects (Arg/Gln; with the Gln residue encoding allele) for the Leiden factor V genotype have improved 30 days survival than homozygotes (Arg/Arg).[39]

GENES RELATED TO VASCULAR PERMEABILITY AND TONUS, FIBROBLASTS ACTIVITY AND SURFACE TENSION

Since ALI/ARDS involve alterations in permeability, vascular tonus, lung injury and repair and, in the ability to keep alveoli open, characterizing a severe respiratory failure picture, the genes involved in this process have an important role. The angiotensin converting enzyme (ACE) is a zinc dependent metalo-peptidase which main role is converting angiontensin-I to angiotensin-II, and bradykinin inactivation. The ACE gene is at the 17q23 locus and has 26 exons. This gene

best known polymorphism consists in insertion (allele I) or deletion (allele D) of an Alu sequence of 287 pairs of bases near to intron 16 extremity 3'. This polymorphic variation produces three possible genotypes: II, ID and DD.[40] Three studies showed an association between these polymorphisms and ARDS mortality, two in Caucasian patients[41,42] and another in Oriental patients.[43] Recently a study in Spain failed to show an association between these polymorphisms and ARDS susceptibility or mortality,[44] a finding which was confirmed by our group.[40] Another polymorphism in the angiotenisinogen gene promoter region (AGT) (-6) A/G, which is directly related to ACE action, did not show an association with susceptibility or mortality.[42]

The vascular endothelial growth factor (VEGF) is a potent vasodilator.[40] VEGF has a 936C>T polymorphism which was studied to determine its participation in genetic ARDS susceptibility. An association study prospectively evaluated 137 normal subjects and 220 MV patients. MV patients were grouped as: ARDS risk (n=103) and ARDS (n=112), and five were excluded from the analysis. The genotypes 936CT and 936TT were significantly more frequent in ARDS patients than in the normal group (P=0.02) and ARDS risk (P=0.03). The 936T allele was more frequent in the ARDS group (P=0.04) compared to the other groups. There was no mortality difference between the groups ARDS risk and ARDS established, however ARDS patients with genotype 936CT and 936TT had a higher Acute Physiologic Chronic Health Evaluation III (APACHE III) than 936CC homozygote patients (P<0.05). These findings suggest that exist an association between 936T allele with ARDS and physiologic disorders, as evidenced by the APACHE III score.[45]

The surfactant protein B (SP-B) is a hydrophobic protein with properties which are crucial for surfactant function. The SP-B encoding gene is at the chromosome 2 short arm, and has about 9,500 base pairs (bp).[46] A polymorphism in this gene intron 4 is associated with ARDS susceptibility.[47] In an ARDS risk population after stratification for gender and adjustments for confounding factors, the SP-B polymorphic variation has shown an association with primary ARDS susceptibility in women, but not in men.[46]

CHEMOTAXIS AND CELL MOTILITY RELATED GENES

Clara cell protein 16 (CC16) is a potent neutrophil chemotaxis and phospholipase A_2 activity inhibitor. An association study with 117 Caucasian ARDS patients and 373 healthy controls failed to show a relationship between the -26G>A polymorphism and ARDS susceptibility.[48]

The Myosin Light Chain Kinase (MYLK) gene importance is related to its participation in the leucocytes apoptosis and diapedesis, two ALI/ARDS essential events.[49] In an association study with a Caucasian subjects group, and another group with Afro-Americans, Gao et al.[50] identified risk for sepsis-induced ALI/ARDS in specific region 5' haplotypes patients for both groups, and on region 3' only for Afro-Americans. ALI following trauma is also influenced by polymorphisms in this gene, particularly among Afro-Americans.[49]

THE ROLE OF GENOMICS IN CLINICAL PRACTICE

The use of association studies information, as every new method, should be careful. For the physician, the initial results of these studies should be confirmed in similar populations by different investigators.[51] Sometimes a given SNP may not show an association, but this should not preclude its disease involvement, as the haplotype based approach with multiple genetic markers may identify an association.[52] The ALI/ARDS genetic epidemiology objectives are to identify genes influencing susceptibility, lung inflammation intensity, need of specific treatments, prognosis and mortality.

To value genetic association studies, a fundamentally important aspect is their quality. This can be evaluated considering: (1) sample size; (2) a suitable control group; (3) Hardy-Weinberg equilibrium; (4) well defined cases for study disease; (5) the sequencing primer should be reproducible; (6) the genetic analysis investigator should not know the subject clinical status (blinding); (7) the study should have statistical power; (8) genotyping should be replicated.[53]

FINAL COMMENTS

The use of genetics for identifying ALI/ARDS risk populations in a different way opens a new field in medicine. The search for improvement of care in the critically ill patients initially involves the identification of candidate genes, which can be done either in experimental or clinic scenarios.The second step is the development of robust and high quality and reproducible association studies.

Care strategies can be established based on such information, since early identification of risk populations until choosing of individualized therapies.

RESUMO

A lesão pulmonar aguda e sua forma mais grave, a síndrome da angústia respiratória aguda, são o denominador comum de várias doenças que podem provocar uma inflamação exagerada nos pulmões. Nos últimos anos, essa variabilidade tem sido atribuída, pelo menos em parte, a fatores genéticos. O presente estudo tem por objetivos revisar o papel dos principais genes envolvidos na suscetibilidade, morbidade e mortalidade na lesão pulmonar aguda e na síndrome da angústia respiratória aguda**.** Através de pesquisa nas bases de dados PubMed e LiLACS, empregando-se os unitermos lesão pulmonar aguda, síndrome da angústia respiratória aguda e síndrome da angústia respiratória do adulto em combinação com polimorfismos genéticos, foram selecionados 69 artigos, dos quais 38 foram incluídos nesta revisão. Foram também considerados artigos relevantes extraídos das referências bibliográficas nos artigos selecionados das bases de dados. Os polimorfismos genéticos são variantes gênicas presentes em pelo menos 1% da população. A presença destas variantes genéticas pode influenciar a expressão de mediadores da resposta inflamatória, afetando diretamente a suscetibilidade à lesão pulmonar aguda, a intensidade da inflamação no parênquima pulmonar, a evolução e o desfecho destes pacientes. Estudos de associação com grandes populações e passíveis de reprodução permitirão de modo definitivo a inclusão da genômica no arsenal diagnóstico, prognóstico e terapêutico de pacientes com lesão pulmonar aguda/síndrome da angústia respiratória aguda

Descritores: Lesão pulmonar; Síndrome da angústia respiratória do adulto; Polimorfismo genético

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