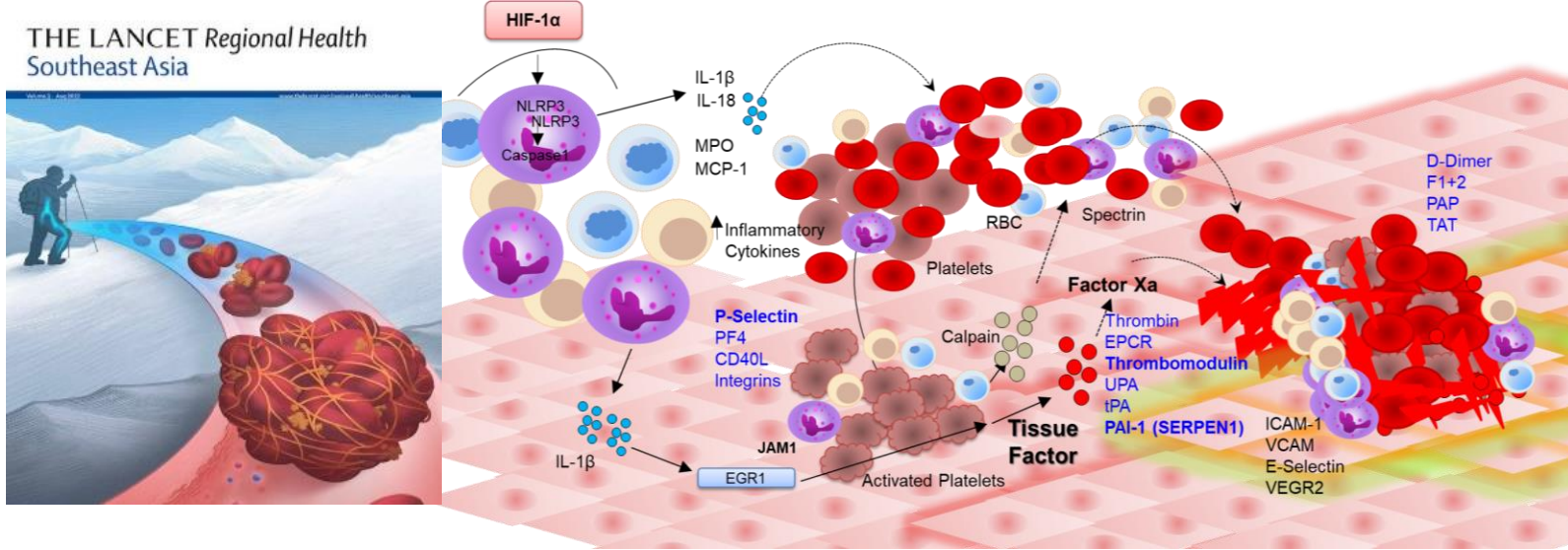


DETAILS OF THE EXCELLENCE IN RESEARCH WORK



Dr. Ashraf has focused his research that was of urgent need and challenge for nation and scientific community to elucidate the blood clotting problem inflicting our soldiers that are positioned at high altitude defending our borders. He remains a pioneer in the field of high altitude thrombosis and has done seminal work in resolving the mystery of blood clotting on exposure to hypoxia (**Lancet Regional Health 2022**). Amongst the major outcomes of his translational research, the landmark work was internationally recognized and published in prominent journal ‘**Blood**’ in 2014, received accolade by an Editorial. The study revealed a novel cause for blood clot formation at altitudes and proposed ‘Calpain’ as a novel biomarker (IPO: 733/DEL/2014) for early diagnosis; thereby providing timely diagnosis to Indian Army Jawans posted at Siachen Glaciers defending our borders (<http://timesofindia.indiatimes.com/india/DRDO-lab-detects-reason-behindthrombosis/articleshow/40139095.cms>).

Dr. Ashraf study has contributed enormously in understanding the etiopathology of clot formation at altitudes, for the development of possible drug targets. He elucidated previously unknown cause of thrombosis at altitudes is centrally regulated by a complex network of coagulatory and NLRP3-inflammasome mediated inflammatory responses. His research established (**PNAS, 2017**) that, hypoxia-inducible Factor-(HIF)-1 α , (**Nobel prize for Medicine 2019**) a protein complex plays an integral role in the body's response to low-oxygen, activates an inflammatory complex inflammasome-NLRP3 and releases inflammatory cytokines like IL-18 and IL-1 β , which eventually causes blood clotting. This novel finding was highly recognized worldwide and published in the ‘**PNAS**’ in 2017; also proposed as potential therapy (*Nature India- doi:10.1038/nindia.2017.143*). The Inflammation-Coagulation-Hypoxemia convolutions has also been observed in COVID-19 pathogenesis, low-molecular-weight heparin have shown encouraging results, therefore natural compound based anticoagulant are also being explore.

In a rare breakthrough, his lab developed a microRNAs mimic based therapy against thrombosis; for the first time the antithrombotic potential of microRNAs was established. These preclinical findings were validated in human patients, supporting the translational significance of miR-145 for development of a novel antithrombotics (IPO:1398/DEL/2015), which could be also tested against COVID-19 infection also. These findings were published in **EBiomedicine (2017)**, a recently established journal in collaboration with *Cell* and *Lancet*.

Dr. Ashraf was the key investigator for one of the biggest longitudinally prospective cohort study carried out by Indian Army and DRDO, involving 1000 infantry Indian Army soldier towards their deployment to Siachen Glaciers recently published in **Lancet Regional Health-South Asia (2022) with editorial commentary**.

His extensive research established the incidence of thrombosis at altitudes were inferentially higher and resulted in convincible recommendation for Indian Army during operational deployment (DGAFMS-15965/4143/2011/DGAFMS/DG-3B/20042011-RESTRICTED). He has also established his leadership qualities by carrying out a multicentric-cross-sectional study on thrombosis involving Army Hospital RR Delhi, Command Hospital Chandimandir, AFMC Pune and DRDO. He has applied this finding on people staying at high altitude regions including native highlanders. Dr. Ashraf's ability to translate his research findings for societal benefit has added new dimensions in the field of high altitude research. The high altitude research contributions were attested by his participation in International consortium for revision of Acute Mountain Sickness diagnosis guidelines.

In summary, Dr. Ashraf has established that hypoxia accelerates a prothrombotic milieu via calpain activation. Thrombus formation is critically regulated by activation of NLRP3-caspase-1-IL-1 β -HIF-1 α axis. The restoration of miR145 levels serves as promising antithrombotic therapy; the seminal contributions for societal benefit, especially for Armed Forces defending our nation. His laboratory is engaged in Machine-Learning Platform development for pharmacogenomics based personalized medicine. His research work found special importance during this pandemic since the COVID-19 virus triggers hypoxemia induced inflammatory cytokines that activates coagulation, the very mechanism was proposed by their team (PNAS, 2017) for blood clotting under hypoxia at altitudes. As a consequence, the therapeutic strategies like Low molecular weight heparin (LMWH) is now widely recommended. The anti-inflammatory properties further make LMWH, a preferred choice in mitigating cytokine storm in COVID-19 patients.

RESEARCH PROFILE

Ongoing Projects: 8

International collaborative Projects: 2

Total Budget: 400 Lakh

Research Publication ~ 60 [PNAS, Blood, eBiomed, Lancet GH]
(7 above IF-10)

Book Chapters: 4

Patents: 2

Citation Indices:

Citations 7766

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Dr. Ashraf's work has a significant impact in both basic and applied aspects of cardiovascular biology and human disease. He pioneered the establishment of a platform for altitude induced thrombotic studies in India. His study on the mechanisms by which thrombus formation is triggered under hypoxia is of immense fundamental importance in our understanding of thrombus formation on ascension to mountains, sports, pilgrimage or other hypoxic environments. Owing to his work, we have now a clear view of about the cause of thrombus formation which remained hidden for the past several decades (Blood, 2014; PNAS, 2017; CATH, 2016; EBiomedicine, 2017). The socio-economic implications of research work carried out by Prof. Ashraf's research group are as follow.

A. Identification of causal role for NLRP3-inflammasome and cytokines (IL-1 β , IL-18) in hypoxia-induced venous thrombosis

Furthermore, it is worth mentioning that Dr. Ashraf's team for the first time demonstrated the expression of tissue factor in rat platelets, and also that its expression is modulated by hypoxia, shedding some light on the mechanism of thrombosis induced by hypoxic environment (Brambilla et al, Thrombosis and Haemostasis, 2015; Camera et al, Seminars in Thrombosis & Hemostasis, 2015). Dr. Ashraf has contributed enormously in understanding the etiopathology of thrombotic episodes in soldiers stationed at extremely HA for the development of possible drug targets. One of his study has established that thrombosis at HA is centrally regulated by a complex network of coagulatory and inflammatory response. This process is critically linked through hypoxia inducible factors-1 α (HIF-1 α). The causal role for NLRP3-inflammasome and IL-1 β in hypoxia-induced venous thrombosis has been the stepping-stone in establishing a direct association between NLRP3 and HIF-1 α during these conditions. This novel finding was highly recognized worldwide with its publication in the *Proceedings of National Academy of Sciences, USA* in 2017 and was also highlighted by Nature India. The work has been greatly applauded and cited by the leading groups like Prof. Alexander Brill, Institute of Cardiovascular Sciences, University of BirminghamUK; Prof. van Budnik, Moscow State Medical University, Moscow; *Trends in Immunology*, 2018.

B. Development of miRNA-145 based therapy against thrombosis.

Dr. Ashraf's lab was also first to propose a microRNA based therapy against venous thrombosis. Using both network based bioinformatics approach and *in vivo* animal model system, his team established the antithrombotic potential of specific small noncoding RNA – microRNA-145 in venous thrombosis. These preclinical findings were validated in human thrombosis patients, supporting the potential of translational significance of miR-145 against VT and development of a novel antithrombotic agents (patent filed with IPO vide no. 1398/DEL/2015). Based on latest information regarding critical role of coagulation pathways in COVID infection and microthrombi formation, this miRNA based therapy could be tested.

C. Discovery of Calpain as Biomarker for early diagnosis of thrombosis at HA

Work done by Dr. Ashraf is especially relevant in India, since the prevalence of thrombosis is comparable to western population is relatively higher in the Himalayan mountain range and it is only Dr. Ashraf's lab where pre-clinical studies and testing is established in Indian Scenario.

Dr. Ashraf has contributed exceptionally well in proposing a novel protein 'Calpain' as a biomarker (Patent filed with IPO vide no. 733/DEL/2014) for early diagnosis of thrombosis and thereby providing timely

treatment to Indian Army Jawans posted at extremely hostile terrain for protecting our borders ([http://timesofindia.indiatimes.com/india/DRDO-lab-detects-reason-behind thrombosis/ article show/ 40139095.cms](http://timesofindia.indiatimes.com/india/DRDO-lab-detects-reason-behind-thrombosis/article-show/40139095.cms)).

By virtue of his findings of Calpain as novel Biomarker, the formation of blood clot can be prevented even at a very early stage. Such discovery of early diagnosis marker is of immense societal benefit as it will significantly reduce the burden of thromboembolic disorders especially in Army Jawans posted at extreme altitudes.

Over all his research has helped in improving the quality life of individuals (either defence personnel, paramilitary forces, native highland and civil population) staying/posted at remote extreme altitude locations like Siachen Glacier, Indo-China Border etc. Nonetheless this will assist in better management and would reduce morbidity and mortality associated thrombotic event in local population, visitors, tourist, and religious pilgrims.

The discovery is very useful for the Hotel & Tourism industry of hilly states like Jammu & Kashmir, Himachal, Uttarakhand and the other North Eastern States where the incidence of this disease is higher than planes.

Dr. Ashraf's contributions, over the years have set out prevalence, pathophysiology, genetic, diagnostic, and development of clinically relevant animal model systems for thromboembolism at HA. He has exclusively established the pre-clinical studies for venous thrombosis in India and demonstrated the translational implications of pre-clinical findings in human patients, which supports the worthiness of the work. Out of the significant outcomes of his translational research, the landmark work internationally recognized, the scientific work published in a prominent journal '*Blood*' in the year **2014**. The work revealed a novel cause for the formation of blood clots on ascension to mountains. This discovery also received an additional accolade by an editorial commentary. In fact, the findings of this work that Hypoxia-induced thrombogenesis is associated with CAPNS1-dependent (Calpain is a calcium-dependent non-lysosomal cysteine proteolytic system) calpain activation in the platelet activation cascade was the basis of the study, which established that Hypoxia interferes with TGF β signaling in macrophages by SMAD2 (Cui et al, Cell & Bioscience, 2015). Dr. Ashraf's team have put forward an interesting set of scientific question to be answered like, specific targeting of this calpain can effectively reduce thrombosis without interfering with hemostasis? (Rafal Pawlinski, Blood, 2014). Furthermore, the work has been significantly commended and cited by the pioneer groups in the area like *APEX 4: high altitude medical research group for Chacaltaya Mountain (5,300m) La Paz, Bolivia; International Hypoxia Symposia, Lake Louise, Canada; International Society for Mountain Medicine*.

D. Establishment of association of genetic polymorphisms with VT manifestations under hypoxia.

The study led by Dr. Ashraf revealed that single nucleotide polymorphisms that are associated with thrombotic episodes in western populations had distinct behavior in Indian population. His research identified the limited role of established genetic variants in imparting susceptibility to VTE in Indian population and thus encourages the identification of novel genetic variants in Indians for the better understanding of the ethnicity based differences in susceptibility of individuals (Thrombosis 2014; Scientific Report 2016). Dr. Ashraf is also known for the exploration of the role of genetic predisposing factors for onset of thrombotic episodes under hypoxia utilizing single nucleotide polymorphisms, microarray, next generation sequencing and bioinformatics approaches (Journal of the Renin-Angiotensin-Aldosterone System 2012; Thrombosis 2014; Scientific Reports 2016; Clinical and Applied Thrombosis & Hemostasis 2017; Thrombosis and Haemostasis 2018). The spectrum of approaches has helped to identify

key genetic factors responsible for predisposing to venous thrombosis. Additionally, study led by Dr. Ashraf demonstrated an association between elevated Plasma endothelin levels of VTE patients with the endothelin-1 polymorphism in Indian population. His research investigations suggested a significant role of endothelin-1 gene polymorphism in individual's susceptibility to the VTE and its clinical progression (Clinical and applied Thrombosis/Hemostasis, 2016). He has also been credited with a pioneering study that implicated noncoding RNAs both small (microRNAs) and long (Lnc-RNAs) in the pathogenesis of thrombosis. The identified leads are being followed for their useful translational benefits.

Dr. Ashraf was the key investigator for one of the biggest longitudinally prospective cohort study carried out by Indian Army (involving 750 volunteers) to elucidate the incidence, prevalence, genetic and molecular basis of HA induced thrombotic disorders in lowlanders stationed at higher altitudes. This study suggested that the incidence of VTE at altitudes were inferentially significantly greater than in the plains. Additionally, this observation has been considered for convincing recommendation in Indian Armed Forces during induction and operational deployments at extreme altitudes (*Project vide DGAFMS - No 15965/4143/2011/DGAFMS/DG-3B/20042011 (RESTRICTED)*).

Apart from his scientific acumen, Dr. Ashraf has also established his leadership qualities by carrying out a multicentric cross-sectional study involving Army Hospital RR Delhi, Western Command Hospital Chandimandir, 153 General Hospital, Leh, AFMC Pune and DRDO Delhi for a comprehensive understanding of this disease. Over all, his research has helped in improving the quality life of individuals (either defence personnel, paramilitary forces, native highland and civil population) staying/posted at remote extreme altitude locations like Siachen Glacier, Indo-China Border etc.

E. Development of Machine Learning (AI) based platform for pharmacogenomics studies, and personalized medicine.

Statins remains the most common drugs for lowering of cholesterol and triglycerides with plethora of evidences supporting their benefits in preventing CVDs in hypercholesterolemia patients. They, in one or the other form, are one of the most widely prescribed medications in the world. But not all patients respond favourably to statin treatment and experience adverse events, this variability in the response to statin is majorly attributed to genetic factors. Polymorphism in few genes have been associated mainly with variability in statins efficacy. We began our study with the retrieval of research paper based on genetic variants studied in response to statin effects from public repository. Tanagra, an open machine learning software for research and academic purposes was then used to for identifying genetic markers that may predict responses to statins and subsequently modify cardiovascular outcomes. In this study, we have deployed a machine learning tool with the ultimate goal of translating pharmacogenetics findings into clinically meaningful translations. As a result of this analysis, general population of patients taking statin could improve treatment adherence and efficacy by creating awareness of their own genetic signature associated with individual pharmacokinetics of statins and the corresponding absolute risk for toxicities. It further reflects on the potential of artificial intelligence in transforming enormous research data into translational application in the form of predictive computational models.

Public writing

12. Aastha Mishra and Zahid Ashraf: [How to live with the virus and fight it: the way ahead](https://www.nationalheraldindia.com) **NATIONAL HERALD**
www.nationalheraldindia.com , May 17, 2020
13. Mohammad Zahid Ashraf COVID-19 pandemic: An opportunity to build assets and develop technologies for future challenges. **TIMES NOW**
<https://www.timesnownews.com/columns/article/covid-19-pandemic-an-opportunity-to-build-assets-and-develop-technologies-for-future-challenges/655900>



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