Review Article

Bovine leukemia virus: a perspective insight into the infection and immunity

Nikbakht Brujeni, Gh.[1*]; Houshmand, P.[2] and Soufizadeh, P.[3]

[1]Department of Microbiology and Immunology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran; [2]Ph.D. Student in Immunology, Department of Microbiology and Immunology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran; [3]Graduated from Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

*Correspondence: Gh. Nikbakht Brujeni, Department of Microbiology and Immunology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran. E-mail: nikbakht@ut.ac.ir

Abstract

Bovine leukemia virus (BLV) is a member of the *Retroviridae* family and belongs to the *Deltaretrovirus* genus. It has a close relationship with human T-cell leukemia virus type I. BLV is responsible for causing enzootic bovine leukosis (EBL), a contagious disease that affects the bovine lymphatic system. This virus poses challenges for the global cattle industry, as it impacts cattle populations all over the world. Despite being widespread and impactful, BLV often goes unnoticed, with many researchers unaware of its presence and the potential consequences it carries. BLV demonstrates varying levels of pathogenicity. The majority of cattle (around 70%) become seropositive asymptomatic carriers, displaying no noticeable clinical symptoms. However, a smaller proportion of infected animals experience persistent lymphocytosis, characterized by an elevated number of lymphocytes in the bloodstream. If not monitored and managed, a subset of these persistently infected cattle may advance to lymphosarcoma. This condition typically presents as tumors in different lymphoid tissues, impacting various organs and overall health and productivity. Furthermore, recent research has highlighted the potential association between the occurrence of breast and lung cancer in humans and the presence of BLV. This review will delve into the recent discoveries concerning BLV, specifically exploring its epidemiology, the economic impact it has on the global cattle industry, its implications for human medicine, and the association between different alleles of the major histocompatibility complex (MHC) and susceptibility or resistance to BLV.

Key words: Bovine leukemia virus, Enzootic bovine leukosis, Major histocompatibility complex, *Retroviridae*

Introduction

The study of bovine leukemia virus (BLV) is a complex and multifaceted endeavor that encompasses various aspects of virology, immunogenetics, disease control, and public health. This virus, primarily affects cattle, has garnered significant attention due to its potential economic implications for the livestock industry and its emerging connections to human health.

BLV is a retrovirus that affects cattle worldwide and causes significant challenges to the livestock industry. Despite its prevalence and impact, BLV is often ignored, with many researchers remaining unaware of its existence and potential consequences. BLV is a member of the *Retroviridae* family, belonging to the *Deltaretrovirus* genus, and is closely related to the human T-cell leukemia virus type I (HTLV-1). It causes enzootic bovine leukosis (EBL), a contagious lymphoproliferative disease (Polat *et al*., 2017a).

In this review, we delve into the intricate world of BLV, from its genomic composition and pathogenicity to routes of transmission and detection methods. We also explore the economic consequences of BLV infection, directly and indirectly, shedding light on its substantial impact on the livestock sector. Furthermore, we examine the potential implications of BLV in human health, discussing the evolving research that hints at a connection between BLV and certain cancers, such as breast and lung cancer. This aspect of the virus underscores the importance of understanding its zoonotic potential and the need for further investigation into its impact on human populations.

The role of immunogenetics in disease resistance and susceptibility is a pivotal aspect of our discussion. We explore the associations between host genetics, particularly the major histocompatibility complex (MHC), and the likelihood of BLV infection. Understanding these genetic factors can guide breeding strategies aimed at producing animals with enhanced resistance to BLV, offering a promising avenue for disease control. Lastly, we emphasize the critical importance of disease control and prevention measures. We draw attention to successful eradication efforts in some European countries, highlighting the importance of

biosecurity measures, diagnostics, and vaccination in these endeavors. We also stress the need for innovation in diagnostic methods and the development of more effective vaccines.

Structure composition of BLV

The virus particle consists of an outer lipid envelope derived from the host cell membrane, enclosing two viral RNA copies. Inside the envelope, the core comprises the structural proteins and the reverse transcriptase enzyme (Kucerova et al., 1999). BLV follows a typical retroviral replication cycle, which begins with viral attachment and entry into the host cell. The envelope protein on the virion's surface interacts with specific cell receptors, facilitating viral entry. Once inside the cytoplasm, the viral RNA genome is reverse transcribed into DNA by the reverse transcriptase enzyme. This viral DNA integrates into the host cell's genome, becoming a provirus. The provirus is then transcribed and translated to produce viral proteins, which assemble into new viral particles. Finally, the newly formed virions are released from the infected cell, ready to infect other susceptible cells (Yamanaka et al., 2022).

Genomic composition of BLV

BLV's genome consists of 8714 nucleotides, which includes three main genetic regions: (1) long terminal repeats (LTRs) at the 5´ and 3´ ends of the viral RNA, (2) the essential structural and enzyme coding region, and (3) pX region. The structural and enzyme coding region contains four crucial loci: gag, pro, pol, and env (Zyrianova and Kovalchuk, 2020). The gag region encodes three mature proteins that are involved in the viral infection cycle, which are p15 (the matrix protein), p24 (the capsid protein), and p12 (the nucleocapsid protein) (Zyrianova and Kovalchuk, 2020). The pol region contains the genetic codes of viral enzymes such as reverse transcriptase, and the env region encodes two major proteins, gp51 (the mature extracellular protein), and gp30 (transmembrane protein) (Polat et al., 2017b). The pX region encodes different types of regulatory and accessory proteins such as Tax, Rex, R3, and G4. These proteins are involved in regulating the viral transcription and maintaining the high viral load in the host cells (Aida et al., 2013). The schematic structure of BLV and its genetic content are shown in Fig. 1. Mutations and recombination within these regions contribute to the genetic variations observed among different BLV isolates. Based on the previous studies, by sequencing the env region, over 11 genotype clusters of BLV have been identified in the world (Polat et al., 2015, 2017a).

Pathogenicity of BLV

BLV infection brings about a series of molecular events that contribute to transforming infected B cells into malignant cells. The viral Tax protein plays a crucial role in this process. Tax regulates viral gene expression and modulates various cellular signaling pathways in cell growth and survival. It promotes cell cycle progression by inactivating cell cycle checkpoint proteins and

stimulating the expression of growth-promoting factors. Additionally, Tax interferes with the host immune response by inhibiting the function of key immune regulators, such as MHC molecules and natural killer (NK) cells (Aida et al., 2013). This evasion of immune surveillance allows infected cells to avoid detection and destruction by the immune system. Furthermore, BLV-induced pathogenesis involves the dysregulation of multiple cellular pathways. The production of inflammatory cytokines and chemokines increases, leading to chronic inflammation and immune dysregulation. The activation of various pro-survival signaling pathways, such as NF-κB and PI3K/Akt, promotes cell survival and resistance to apoptosis, contributing to the accumulation of malignant cells. While BLV can infect different types of immune cells, tumors caused by BLV typically originate from the CD5+IgM+B cell subpopulation (Gillet et al., 2007).
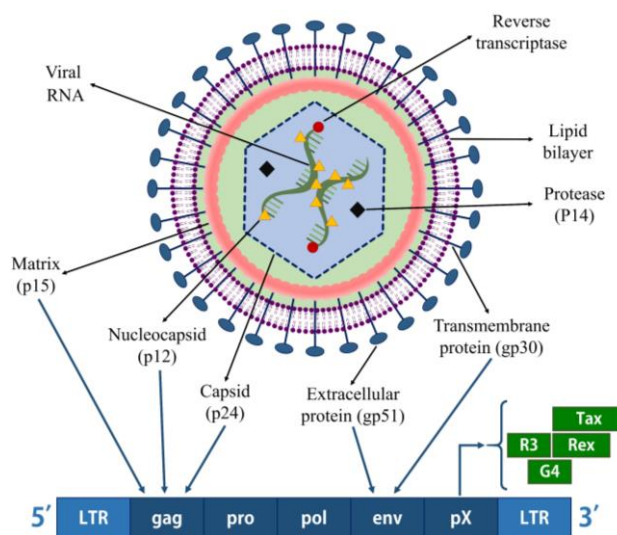

Fig. 1: The structure and genomic composition of BLV. As mentioned in the text, the BLV genome is made up of three main regions: long terminal repeats, the structural and enzyme coding region (including four significant loci known as gag, pro, pol, and env), and the pX region

The clinical signs of leukosis can manifest in different ways, such as reduced strength or overall weakness, decreased appetite, digestive problems, chronic bloating, displacement of the abomasum, changes in bowel movements, swelling of superficial lymph nodes, reduced milk production, mobility issues, paralysis, weight loss, and occasionally, neurological symptoms (Polat et al., 2015). Upon infection, most cattle (about 70%) become seropositive asymptomatic carriers, showing no apparent clinical signs. However, a small percentage of infected animals develop persistent lymphocytosis, characterized by an increased number of lymphocytes in the blood. If left unchecked, a subset of these persistently-infected cattle may progress to lymphosarcoma. This disease typically develops tumors in various lymphoid tissues, affecting multiple organs and compromising overall health and productivity. The determinants of pathogenicity still need to be understood,

but several virulence factors have been identified. The Tax protein, encoded by the viral genome, plays a key role in promoting viral replication and immune evasion. Additionally, host factors (such as MHC alleles) and the interplay between the virus and the host immune response contribute to disease progression (Aida *et al*., 2013).

Routes of transmission of BLV

The primary mode of BLV transmission in cattle is through the exchange of infected blood. This typically occurs during activities that involve direct contact between animals, such as aggressive behavior resulting in biting or licking wounds. Additionally, using contaminated needles and surgical instruments can transfer the virus from infected to susceptible individuals (Juliarena *et al*., 2016). Another significant transmission mode is through the consumption of colostrum and milk from infected cows. BLV can be present in the mammary secretions of infected cows, allowing the virus to transfer to their offspring during nursing. Calves can become infected with BLV through the ingestion of colostrum or milk from an infected dam (Hopkins and DiGiacomo, 1997). BLV can also be transmitted through vertical or transplacental transmission from infected dams to their offspring during the pregnancy period. The virus can cross the placental barrier, infecting the developing calf in the womb. Vertical transmission may result in the infected calf (Juliarena *et al*., 2017). Insects, such as biting flies and ticks, can act as mechanical vectors for BLV transmission. These insects can carry the virus on their mouthparts or bodies after feeding on infected animals (Juliarena *et al*., 2017). Major BLV transmission routes in cattle are shown in Fig. 2.

Detection methods and prevalence of BLV

So far, various methods have been utilized for the detection of BLV. The function of these methods is based on identifying viral antigens, genetic material or serum anti-BLV antibodies (Nikbakht Brujeni *et al*., 2007, 2011; Nikbakht Brujeni, 2009). Table 1 demonstrates some of these methods along with their target molecules.

Several studies have shown the high prevalence of BLV in different regions of the world. A study stated that the prevalence of this virus in the US was 40% (Ladronka *et al*., 2018). Another study has shown that in Argentina, 84% of dairy cows have specific antibodies against this virus within their blood (Polat *et al*., 2017a). A meta-analysis study, which evaluated nearly 35,000 cows, demonstrated that 10% of cows in China are BLV seropositive (Ma *et al*., 2021). Also, two other studies indicated the presence of seropositive cows in Turkey and Mexico (Şevik *et al*., 2015; Heinecke *et al*., 2017). In Egypt, based on the results of serological tests, it is stated that 15.83% of Egyptian dairy cows are BLV
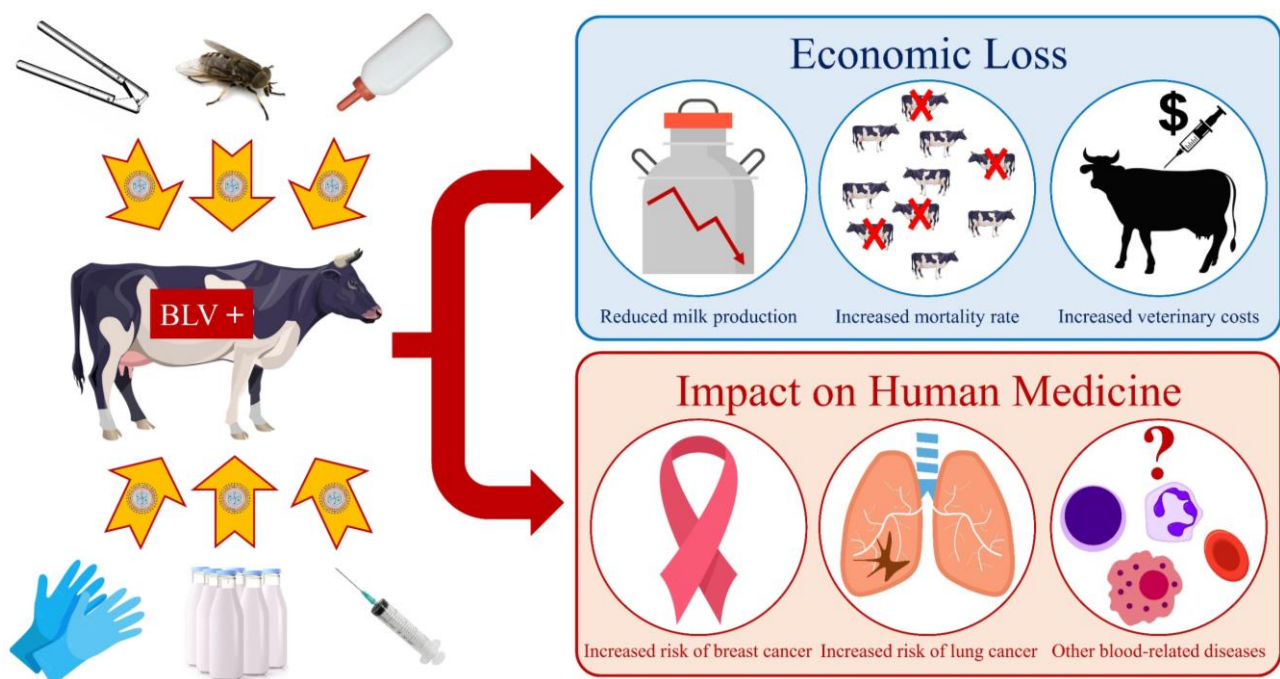

Fig. 2: The main ways of BLV transmission within farms, and the resulting economic losses and health effects. The main factors that contribute to the transmission of BLV within a herd include cows being exposed to contaminated blood, insect bites, and the consumption of milk and colostrum from infected cows. A major challenge in controlling the spread of BLV is that many infected animals do not show noticeable clinical symptoms, allowing for continuous virus transmission within the herd. The economic losses resulting from the spread of BLV include decreased milk production in the herds, increased mortality of young cows, and additional expenses for treating and replacing culled animals. Furthermore, numerous studies have examined the implications of BLV outbreaks on human health. It has been noted that BLV can be identified as a risk factor for breast and lung cancer. Moreover, since BLV proviral genes have been detected in human blood cells, there might be a potential connection between this virus and other blood-related diseases, which should be investigated

Table 1: Common methods that have been utilized for the detection of BLV

Category	Method	Target molecule	Reference
Molecular methods	Nested-PCR	gag gene	Nikbakht Brujeni *et al*. (2010, 2016)
	Microarray assay	Milk small extracellular vesicle mRNA	Hiraoka *et al*. (2022)
	Southern blotting	gag gene	Nikbakht Brujeni *et al*. (2010)
Immunologic methods	Serum neutralization	Serum antibody	Porta *et al*. (2019)
	Indirect ELISA	Serum antibody	Mohammadi *et al*. (2011)
	Western blotting	gp51, gp30, p24, envelope glycoproteins	Tajima *et al*. (1998) and Nikbakht Brujeni *et al*. (2006)
	Agar gel immunodiffusion	Serum antibody	Roberts *et al*. (1989)
	Immunohistochemistry	p24	Buehring *et al*. (2014) and Maezawa *et al*. (2022)
	Immunochromatography	Serum antibody	Barshevskaya *et al*. (2019)
	Immunoprecipitation	Lymphosarcoma (tumor) antigen	Nikbakht Brujeni *et al*. (2008)
Other methods	Electron microscopy	Virion	Calafat and Ressang (1977)
	Biosensor (based on ZnO nanorods photoluminescence)	Serum antibody	Ruban *et al*. (2017)
	Biosensor (based on surface-enhanced raman scattering)	gp51	Baniukevic *et al*. (2013)
	Biosensor (based on surface plasmon resonance)	Serum antibody	Klestova *et al*. (2019)

seropositive (Heinecke *et al*., 2017). Many European countries, such as England, Belgium, France, Spain, and Sweden, have succeeded in becoming officially free of BLV by implementing strict control programs. However, there are still reports of this disease in some other countries, such as Italy and Portugal (Bartlett *et al*., 2014).

Recently, multiple studies reported the circulation of BLV in Iranian cattle. Nikbakht Brujeni *et al*. (2016) conducted a study where they collected 190 samples from calves in three dairy farms located in various regions of Iran. Their findings revealed that 36.8% of these samples tested positive for BLV antibodies. Also, among the studied samples, 21.6% showed persistent a lymphocytosis profile, while 15.2% displayed lymphosarcoma profile (Nikbakht Brujeni *et al*., 2016). In another study, the presence of BLV gag gene in the apparently healthy Holstein cows in Tehran was examined by nested PCR. The results demonstrated that 16.8% of samples were positive (Nikbakht Brujeni *et al*., 2010a). In another research that was conducted to investigate the prevalence of BLV in central, western, and eastern regions in Iran, the examination of 1619 serum samples from Iranian cows showed that 16.73% of the cows were positive for the presence of anti-BLV antibodies (Nikbakht Brujeni *et al*., 2010b). A seroepidemiological survey of BLV infection in some dairy farms of Iran showed that the overall prevalence of BLV infection within Iranian cattle was 29.9%. It was also demonstrated that in general dairy farms, the prevalence of BLV infection was statistically higher compared to private dairy farms (Mohammadi *et al*., 2011). In a different study conducted in various regions of Iran, researchers collected 882 serum samples. They found that 16.2% of these samples tested positive for antibodies using the ELISA method (Nikbakht Brujeni *et al*., 2015). Another study revealed that 22.3% of the cows slaughtered at a slaughterhouse in Tehran tested positive for anti-BLV antibodies. Additionally, this research demonstrated a significant positive correlation between the age of cattle and BLV infection, as well as decreased CD4 + T lymphocytes in BLV-infected cattle compared to healthy ones (Tooloei *et al*., 2009). It is important to take into account co-infection with other viruses alongside BLV. For instance, a study has mentioned the co-infection of BLV and the bovine immunodeficiency virus (Bazargani *et al*., 2010).

The mentioned studies highlight the importance of considering the circulation of BLV within Iranian cattle and controlling its transmission.

Economics of leucosis

Cattle play a vital role in the livestock industry, serving as valuable assets for human use in both traditional and modern agricultural sectors. Providing these animals with a stable and secure environment is essential to maximize their productivity. BLV, as previously mentioned, can severely impact on the immune system of calves. The immune system plays a dual role, acting as a defense mechanism against infectious agents while consuming significant body resources (Segerstrom, 2007). When infected with BLV, about 30% of cows may experience persistent lymphocytosis, leading to increased energy consumption by their immune system due to the high rate of lymphocyte proliferation. This energy could be used to produce livestock products such as milk and meat under natural conditions. Additionally, the involvement of B lymphocytes and a weakened immune system create favorable conditions for the growth and colonization of other infectious agents in the body, further intensifying the immune response and creating a defective cycle of increased energy consumption by the immune system (Olaya-Galán *et al*., 2022). The aforementioned cycle can result in economic losses for the livestock industry, both directly and indirectly.

The direct economic losses caused by BLV are result from virus directly affecting infected livestock. Infected animals, if detected, may be culled at a young age and not live their full lifespan. Additionally, the immune system's heightened activity and secondary bacterial and viral infections resulting from weakened specific immunity reduce the energy and protein available for milk production, decreasing in milk production (Gross, 2023). Although some previous studies have shown that individual cows infected with BLV may experience increased milk production, at the herd level, milk production decreases (Norby *et al*., 2016). It has been estimated that in the United States alone, the 40% prevalence rate of BLV results in approximately $525 million in annual losses solely due to reduced milk production (Otta *et al*., 2003). Similarly, other countries

with high BLV prevalence rates are expected to experience significant annual losses due to decreased milk production. The same holds true for the production of meat. A study that was conducted in Japan examined the impact of BLV on carcass weight reduction, revealing that infected animals with high proviral load had an average carcass weight reduction of 30.4 kg compared to healthy animals. Based on this data and the number of BLV-infected animals culled in this region, it is estimated that approximately $1.3 million was lost in 2017 due to reduced meat production caused by BLV infection (Nakada *et al*., 2022). In another study, it was determined that in a herd with a 50% prevalence of BLV, and considering that approximately 2% of affected animals develop lymphosarcoma, an estimated annual cost of $6,400 per 100 cows is required for the treatment of lymphosarcoma (Erskine, 2009).

However, the economic losses associated with bovine leukemia virus (BLV) are not solely a result of direct causes. Some economic losses are indirectly caused by the contamination of livestock with BLV. Culling of infected animals requires either replacing them with healthy ones or providing compensation. Unfortunately, indirect economic losses have often been overlooked in various studies (Juliarena *et al*., 2017; Nakada *et al*., 2023). Additionally, diagnostic tests like PCR and ELISA to detect the virus in large herds, which necessitates a significant number of samples, can be quite costly. Another category of indirect economic losses is linked to products derived from seropositive livestock that do not exhibit clinical symptoms. Numerous studies have demonstrated that BLV genetic material can be present in milk and other livestock products, rendering it impossible to export these products to countries where BLV has been eradicated, such as European Union countries (Juliarena *et al*., 2017). Another form of indirect damage is the reduction in livestock production. A study has indicated that animals infected with BLV have a 2.61 times higher risk of subclinical mastitis compared to healthy animals. The development of mastitis in these animals leads to an increase in somatic cell count (SCC) in milk, making it unacceptable for use in the dairy industry. According to this study, it is approximated that BLV-induced mastitis resulted in around $6 million in damages in the Hokkaido region of Japan in 2017 (Nakada *et al*., 2023).

Based on the data mentioned above, it is crucial to prioritize herd health and adhere to biosecurity measures to mitigate the transmission of BLV. In order to accurately assess the direct and indirect impacts of BLV, it is also imperative to gather precise data on the disease prevalence in developed and developing nations. Fig. 2 illustrates the economic losses associated with BLV.

The importance of BLV in human health

Researchers have explored the potential harm caused by BLV in humans for decades. As we mentioned earlier, BLV has a close relation with HTLV-1. Understanding the retroviral cycle led to the hypothesis that, similar to other retroviruses, BLV might be capable of infecting humans and causing harmful effects (Buehring *et al*., 2014). Consequently, shortly after BLV was discovered, multiple studies were carried out to explore its potential to cause human illness.

Over time, as more sensitive diagnostic methods like ELISA and PCR were introduced, researchers in this field began to reconsider their beliefs. Contradicting earlier findings, BLV proteins and genetic material were discovered in raw dairy products and human tissues. In an early report, Nikbakht Brujeni *et al*. (2010b) found that the overall prevalence of anti-BLV antibody in human serums, collected from different cities in Iran, was 12.5% (57/454). In the following step, out of 57 samples that were detected positive via ELISA, seven samples were detected to be positive for the presence of the BLV gag gene based on the Nested PCR (Nikbakht Brujeni *et al*., 2010b). Bartlett *et al*. (2020) estimated that approximately 70% of humans had anti-BLV antibodies in their serum, while around 25% had detectable provirus in their blood. Subsequent studies revealed the presence of anti-BLV antibodies in individuals who had not been in direct contact with livestock. This finding led to the suspicion that the virus's proteins and genetic material might be transmitted to humans through food and dairy products (Bartlett *et al*., 2020).

Once the virus antigen was found in dairy products and the presence of anti-BLV antibody was confirmed in human serum, renewed attention was given to the potential pathogenicity of this virus in humans. As a result, numerous studies have been conducted worldwide to further investigate this matter. One study confirmed the existence of BLV genetic material in human breast tissue (Buehring *et al*., 2014). Another study conducted in Minas Gerais, Brazil, aimed to explore the connection between breast tumors and BLV. It revealed that BLV proviral genes were present in 95.9% of samples from tumorous breasts and 59% of healthy breasts (Delarmelina *et al*., 2020). In another research, a total of 2710 breast samples were collected from individuals with breast cancer as well as healthy individuals. The findings of this research demonstrated that 26.8% of samples taken from breast tumor patients contained BLV genes, whereas only 10% of samples from healthy breasts contained BLV genes (Khan *et al*., 2022). In 2019, a review article consolidated and analyzed the results of four previously published studies investigating the connection between breast tumors and BLV. Based on the data and statistical analysis, the average odds ratios for the presence of BLV in tumor samples compared to healthy samples were calculated to be 4.01 (Buehring *et al*., 2020). While these studies do not definitively establish a direct link between BLV and breast cancer, they do suggest that BLV could potentially be a contributing factor or risk factor for the development of breast cancer.

In addition to breast tissue, previous studies have demonstrated the detection of BLV proviral genes in human lung and blood cells. Additionally, it has been

observed that this virus is capable of infecting certain human cell lines, such as human lung embryonic cells (WI-38), suggesting the presence of specific entry receptors on these cells (Robinson *et al.*, 2016; Buehring *et al.*, 2019). Two additional studies have contributed to our comprehension of how this virus might infect humans. The first study demonstrated that BLV can naturally circulate in cattle, buffalo, and sheep. This inter-species transmission is crucial to zoonotic diseases (Olaya-Galán *et al.*, 2022). The second study focused on extracting and amplifying the BLV *env* gene from healthy and cancerous breast samples in humans and cow blood samples in a specific geographic region. The researchers discovered a genetic similarity of 97.8 to 99.7% between the viruses obtained from cows and humans. This discovery further supports the hypothesis of BLV being a zoonotic agent (Fig. 2) (Canova *et al.*, 2021).

These instances emphasize the importance of further examining the zoonotic aspects of BLV. It is crucial to conduct additional studies to explore the potential connection between BLV and the prevalence of various cancers in humans. Furthermore, it is essential to provide proper education and training to farmers and ranchers to prevent the consumption of raw dairy products, stressing the importance of pasteurization.

Associations of immune response genes with susceptibility or resistance to the BLV

The susceptibility or resistance to diseases is influenced by host factors (Stear *et al.*, 2012; Ali *et al.*, 2019). Despite being raised under similar conditions within the same herd, individual farm animals may exhibit significant variations in their response to infectious agents. When exposed to a certain pathogen, some of them may show severe clinical symptoms, while others may be completely asymptomatic. The major histocompatibility complex (MHC) has been identified as a crucial factor in determining the host's susceptibility or resistance to pathogenic agents, making it one of the most significant elements in this regard (Nikbakht Brujeni *et al.*, 2016, 2022).

MHC is a cluster of ancient genes that plays a crucial role in the immune system by distinguishing between self and non-self. The MHC classical class I and II molecules bind to and present peptide fragments to T lymphocytes. The MHC also has significant roles in cytokine production, autoimmunity, reproductive success, and productivity (Nikbakht Brujeni and Esmailnejad, 2015; Esmailnejad and Nikbakht Brujeni, 2016; Alkaragoly *et al.*, 2018; Ali *et al.*, 2019). The high variability and somatic variations in MHC genes allow hosts to recognize numerous foreign peptides and direct immune responses. In veterinary science, the MHC's important role in disease resistance and production traits makes it a precious marker in selection programs (Behl *et al.*, 2012; Stear *et al.*, 2019; Nikbakht Brujeni *et al.*, 2022).

Bos taurus (cow) is one of the farm animals that has received significant research attention regarding its MHC. Cattle MHC or bovine leukocyte antigen (BoLA) is situated on chromosome 23 and consists of a minimum of 154 functional genes (Behl *et al.*, 2012). Some regions of BoLA have a huge amount of allelic polymorphism (Alkafajy *et al.*, 2020). For instance, the second exon of *BoLA-DRB3* gene has 384 identified alleles. Several previously published articles have investigated the association between different BoLA alleles and susceptibility or resistance to pathological conditions such as foot and mouth disease (FMD), mastitis, theileriosis, and gastrointestinal parasitic infestation (Behl *et al.*, 2012). Considering the huge economic losses caused by bovine leukosis, multiple papers have also evaluated the association between BoLA alleles and susceptibility/resistance to BLV. Based on the prior findings, BoLA class II alleles, especially alleles of the second exon of the *DRB3* gene, have a significant association with the development of sensitivity/resistance to BLV (Nikbakht Brujeni *et al.*, 2016).

In three studies, some of the BoLADRB3.2 alleles have been reported to be associated with resistance (DRB3.2 *0902, *0701, and *0703) or susceptibility (DRB3.2 *1201, *1501, *1503, *1101, *0101, and *0102) to persistent lymphocytosis in Holstein-Friesian cattle (Xu *et al.*, 1993; Lewin *et al.*, 1999; Panei *et al.*, 2009). In another study, it was stated that cows with the DRB3.2*11 allele, which is associated with resistance to persistent lymphocytosis, exhibited a considerably lower number of BLV-infected B cells compared to cows of similar age and seroconversion status but with DRB3 alleles associated with persistent lymphocytosis susceptibility (Mirsky *et al.*, 1998). Among Japanese Holstein cows, the most important allele which is reported to be associated with resistance to high proviral load (the insertion of virus genetic material into the host DNA) is DRB3*009:2, followed by DRB3*002:01, and DRB3*014:01:01. On the other hand, DRB3*012:01 is reported to be a susceptibility-associated allele (C.-W. Lo and Aida, 2022). Hernandez *et al.* (2018) found that DRB3.2*1101 is associated with persistent lymphocytosis resistance in Colombian Harton cattle, while *25011 and *2703 are associated with persistent lymphocytosis susceptibility.

We have also investigated the association of different profiles of BLV infection with BoLA-DRB3.2 alleles in Iranian Holstein cattle (Fig. 3). Based on our findings, DRB3.2*0101, *1101, and *4201 alleles were associated with susceptibility to persistent lymphocytosis, while cattle with *3202 allele were resistant to persistent lymphocytosis. Also, we discovered a significant association between BoLA-DRB3.2*1802, *3202, and *0901 alleles and susceptibility to BLV-induced lymphosarcoma. On the other hand, alleles like *0101 and *1101 were associated with having better resistance against lymphosarcoma (Nikbakht Brujeni *et al.*, 2016). In another study conducted by our team, samples were collected from two herds of cattle, one of which was
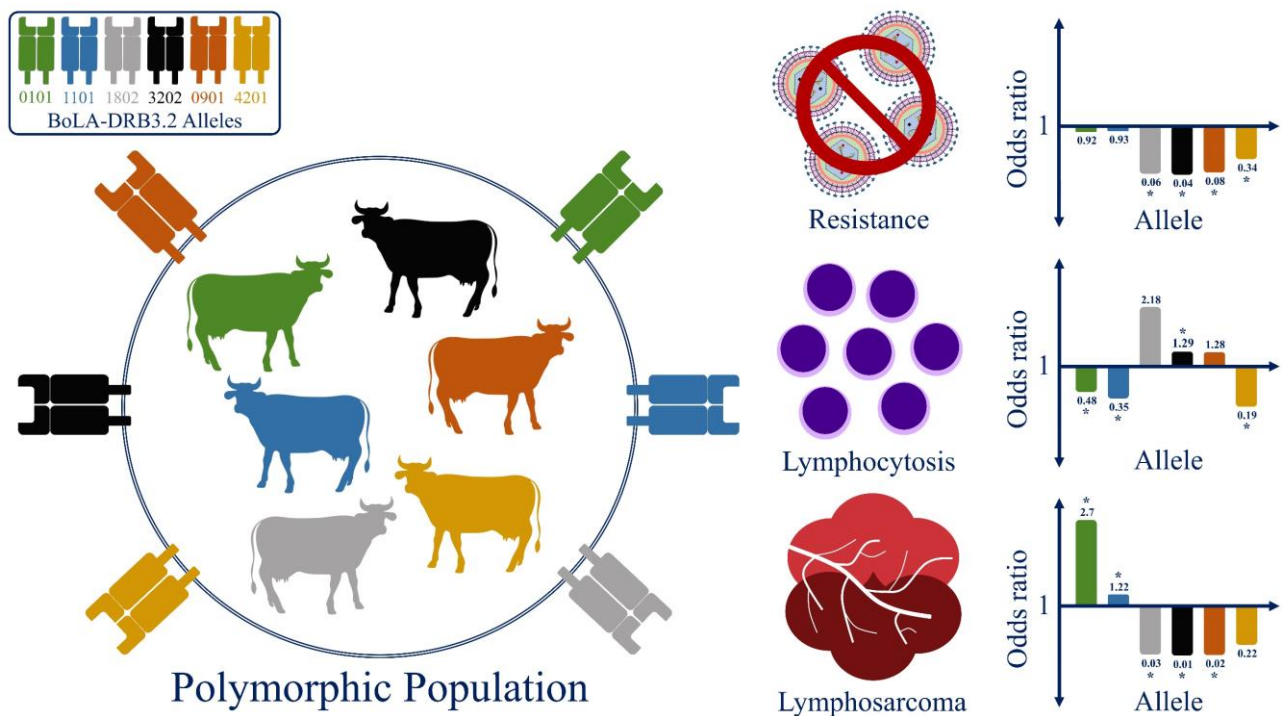
Fig. 3: Association between MHC alleles and susceptibility/resistance to BLV. Various studies have revealed that certain MHC alleles, particularly those found in the second exon of the *DRB3* gene of MHC class 2, exhibit a noteworthy association with the occurrence of different BLV profiles in cattle. For instance, Nikbakht Brujeni *et al*. (2016) demonstrated that the BoLA-DRB3.2 *0101 allele is associated with susceptibility to the persistent lymphocytosis profile while conferring resistance to the lymphosarcoma form. Other numbers and alleles shown in the figure are also real and drawn based on the mentioned article

Table 2: Alleles of BoLA-DRB3.2 that have been stated to be associated with susceptibility/resistance to the profiles of BLV in different regions of the world

BLV profile	Region	Cattle breed	Number of cattle	DRB3.2 allele type	Effect	Reference
PL*	Argentina	Holando-Argentino	81	*11, *23, *25, *28, *40	PL resistance	Panei *et al*. (2009)
				*22, *24	PL susceptible	
	Iran	Holstein Friesian	190	*3202	PL resistance	Nikbakht Brujeni *et al*. (2016)
				*0101, *1101, *4201	PL susceptible	
	Colombia	Colombian Harton	93	*1101	PL resistance	Hernandez *et al*. (2018)
				*25011, *2703	PL susceptible	
LS**	Iran	Holstein Friesian	190	*0101, *1101	LS resistance	Nikbakht Brujeni *et al*. (2016)
				*1802, *3202, *0901	LS susceptible	
	Japan	Holstein Friesian	832	*1001, *1101	LS resistance	Lo *et al*. (2020)
	Japan	Japanese Black	333	*1101	LS resistance	Lo *et al*. (2021)
				*0502, *1601	LS susceptible	

* PL: Persistent lymphocytosis, and ** LS: Lymphosarcoma

BLV-seropositive, and the other was BLV-seronegative. The results revealed a notable difference in the prevalence of MHC alleles associated with susceptibility/resistance to the BLV between the two herds (Lotfollahzadeh *et al*., 2014). Table 2 summarizes the DRB3.2 alleles that have been reported to be associated with susceptibility/resistance to the BLV profiles in different regions of the world.

Considering that the complete eradication of BLV using biosecurity measures seems to be very difficult in many countries, breeding animals that genetically have alleles associated with resistance to BLV can be a suitable alternative.

Disease control and prevention

Prevention is key role in controlling the spread of BLV in cattle herds. Disease control or altering the situation to a norm, standard or desired *status quo* can be reached in several ways: management and rearing measures, immunization, and decisions for improved disease resistance. Implementing strict biosecurity measures, such as maintaining a closed herd system and preventing the introduction of infected animals, can help reduce the risk of BLV transmission. Proper hygiene practices, including using sterile needles and surgical instruments, are essential to prevent iatrogenic transmission. Regular testing and culling of persistently infected animals can also help limit the spread of BLV within the herd (Rodríguez *et al*., 2011). Although most efforts to produce vaccines with sufficient efficacy and effectiveness against BLV have failed, multiple attenuated vaccines have been made to control this disease. Genetically modified strains of the virus have

been used in these vaccines to reduce the pathogenicity and virus shedding. For instance, Willems *et al.* (1994) developed two BLV strains with attenuated phenotype, one of them with a point mutation in the transmembrane protein gene, and the other one with a partial deletion of the R3-G4 sequences. More vaccines will be needed to control BLV outbreaks shortly.

In the case of improving disease resistance, it is supposed that natural selection by pathogenic pressure has not resulted in the selection of resistant animals and the elimination of all susceptible animals. Therefore, disease control should be programmed based on the relative cost-benefits and effective immune responses (Nikbakht Brujeni, 2022). The potential to increase in numbers, as a struggle for existence, will increase the potential of the genetic variation within a species. It is not surprising that the high level of selection for a few economically important traits decreased the genetic diversity in commercial breeds. Although natural selection may increase the frequency of immune genes that improve reproductive success, in the commercial breeding sense, disease control programs should have a look at the genetically based immune responses. Breeding based on immunogenetics data can reduce disease prevalence and help in vaccine design (Nikbakht Brujeni *et al.*, 2022).

A practical approach for improving animal health and production is genetic selection. Based on marker-assisted selection, detection of linkage between DNA markers and loci associated with production and immune traits is preferred. MHC is a candidate genetic region for controlling disease resistance and immune responses in human and animals (Nikbakht Brujeni *et al.*, 2022). We studied the associations between *MHC* gene polymorphisms and immunity in cattle. We aim to show the association between MHC alleles and important production and reproduction traits in the future. Our results strengthen the hypothesis that immunogenetics provides precious designs for keeping natural resources and replacing detrimental therapeutic materials with minimal environmental threats.

Conclusions and future perspective

Given the widespread presence of BLV in numerous parts of the world, it is essential to prioritize the management and elimination of this virus nationally and globally. The existing studies that discuss the negative impact of BLV on the livestock sector predominantly focus on developed nations, overlooking the substantial economic losses on a global scale that surpass the currently available data.

Furthermore, recent research in the field of human medicine has demonstrated the association between the virus infection and a higher incidence of breast and lung cancer. Hence, it becomes evident that managing the infection holds significance not only in terms of veterinary medicine and animal husbandry but also in improving human health and well-being. The positive impact of disease control will enhance the overall quality of human life. There are multiple envisioned approaches to prevention or control, which can yield highly effective results when implemented in combination and simultaneously:

1- One approach is to leverage the successful experiences of European nations that have effectively eradicated this virus within their borders. It is crucial to adhere to herd health principles and promptly isolate animals displaying potential clinical symptoms or identified through available paraclinical diagnostic methods from the rest of the healthy population. Additionally, the culling of infected animals plays a vital role in the eradication process.

2- The present diagnostic techniques, notably ELISA and PCR, are highly accurate regarding sensitivity and specificity. However, their drawback lies in being time-consuming, and time is of utmost importance in eradicating BLV. There is a pressing need to innovate and develop new diagnostic methods that can be readily implemented on farms, such as biosensors and rapid tests. These advancements would significantly reduce the time required to differentiate infected animals from their healthy counterparts.

3- In the battle against infectious agents, a crucial approach is utilizing efficient and effective vaccines. However, only a limited number of vaccines have been successfully developed for BLV. Since, BLV can persistently infect an animal's immune system, resulting in persistent lymphocytosis, developing vaccines that offer prolonged protection becomes essential. Thanks to advancements in reverse vaccinology, there has been a recent opportunity to identify and utilize viral antigens with strong immunogenic properties. This method has opened up new possibilities in identifying antigens that can serve as effective immunogens.

4- Given that the association between the host's genetic factors, like MHC alleles, and their susceptibility or resistance to various infectious agents has been established, developing animals that are resistant to harmful pathogenic agents like BLV appears to be a highly effective strategy. This approach holds great potential, particularly for countries facing financial constraints and limited resources to implement comprehensive biosecurity measures on farms.

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Conflict of interest

The authors declare that they have no conflict of interest.

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